ALKYLALUMINUM DERIVATIVES AS OXOPHILES IN ORGANIC SYNTHESIS: STRUCTURE AND REACTIVITY STUDIES

BY

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR DEGREE OF DOCTOR OF PHILOSOPHY

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To my parents, with thanks
for their never ending
support and encouragement

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Chairman: Merle A. Battiste
Major Department: Chemistry

A new synthetic approach for the more volatile *alpha*-vinyl oxiranes required for subsequent studies with organoaluminum reagents has been developed. This the Horner-Wittig reaction of diphenylphosphinoyl-methyl lithium with α,β-unsaturated ketones, e.g. 2-cyclohexen-1-one, is the key step in the sequence producing stable crystalline intermediates, in contrast to previous schemes in which volatile liquids are realized at each stage. These solid intermediates can then be stereoselectively epoxidized with MCPBA to give a penultimate crystalline precursor to the desired vinyl oxirane. Treatment of this 2,3-oxido Horner-Wittig intermediate under basic conditions results in the loss of the diphenylphosphinoyl group as the water soluble phosphinous acid, thus simplifying final workup and isolation of the volatile

vinyl oxiranes. The synthetic sequence as presented proceeds with good to excellent yields.

The reaction of diethyl-carbo-*tert*-butoxymethyl-alane (Rathke alane, RkeAl) with vinyl oxiranes has been studied in order to determine the necessary stoichiometry for optimum yields of the product hydroxy ester. Several NMR studies were carried out in an attempt to elucidate the structure of the RkeAl in tetrahydrofuran (THF) solution. A mechanism for the reaction of RkeAl with vinyl oxiranes is proposed based on the reactivity and structural investigations. Reactions of the RkeAl with aldehydes and ketones were also demonstrated to proceed with good yields. Structural variations of the ester moiety of the alane were investigated in order to expand the reagent's applicability to organic synthesis. Preliminary studies on chiral induction via the RkeAl type reaction are described.

Formation of alkenes through the thermal reaction of trimethylaluminum with ketones, an overlooked reaction, has been demonstrated. The possible synthetic utility of this reaction may be seen in the formation of 2-methylcamphene in one step from camphor in high yield. Reaction conditions are described for alkene isolation for several ketones. A mechanism for the formation of these alkenes is offered.

CHAPTER I

INTRODUCTION

The field of organometallic chemistry has undergone a tremendous surge in popularity in research over the last quarter century. One of the main goals of this research has been the development and application of organometals as synthetic reagents for selective organic transformations. In particular, investigations into the application and scope of organoaluminum compounds has garnered significant interest due to their application in natural product synthesis and their somewhat unique properties.[1] As early as 1955 aluminum alkyl species were noted to exhibit unusual behavior.[2] Aluminum alkyls, R_3Al, react with carbonyl compounds in an analogous fashion to that of Grignard reagents; however, only a single aluminum-carbon bond reacts in an additive fashion, leaving the remaining two alkyl substituents deactivated. This deactivation is associated with bond formation in the product between aluminum and the oxygen atom of the former carbonyl group, but the precise reasons for the greatly reduced reactivity of

the remaining aluminum bound alkyls is still open to speculation.

In general, organometallic compounds may act as either a Lewis acid or as a nucleophile in their reactions with carbonyl compounds and oxiranes. From an antithetic standpoint oxiranes are seen to have greater synthetic potential than carbonyl compounds owing to their greater flexibility as starting materials for advanced syntheses since two carboncenters are available for substitution, rather than one. In addition two different pathways are available for the reaction of saturated oxiranes with organometals: 1) direct addition resulting in two possible isomeric alcohols; 2) rearrangement to either the aldehyde or ketone and subsequent addition to the resulting carbonyl group. The pathway taken can be dependent on the metal atom involved and the structural (steric) environment of the oxirane sites. For example, nucleophilic ring opening at the least hindered site of an epoxide is generally the main reaction seen with alkyl cuprates,[3] whereas trialkylaluminums yield predominantly the addition product resulting from ring opening and addition to the more substituted site.[4] Also seen in some of these reactions are products resulting from rearrangement and subsequent addition. Reactions involving trialkylaluminum reagents appear to be

sensitive to the choice of reaction solvent and conditions as demonstrated by the reaction of styrene oxide with trimethylaluminum as shown in Figure 1-1.[5]

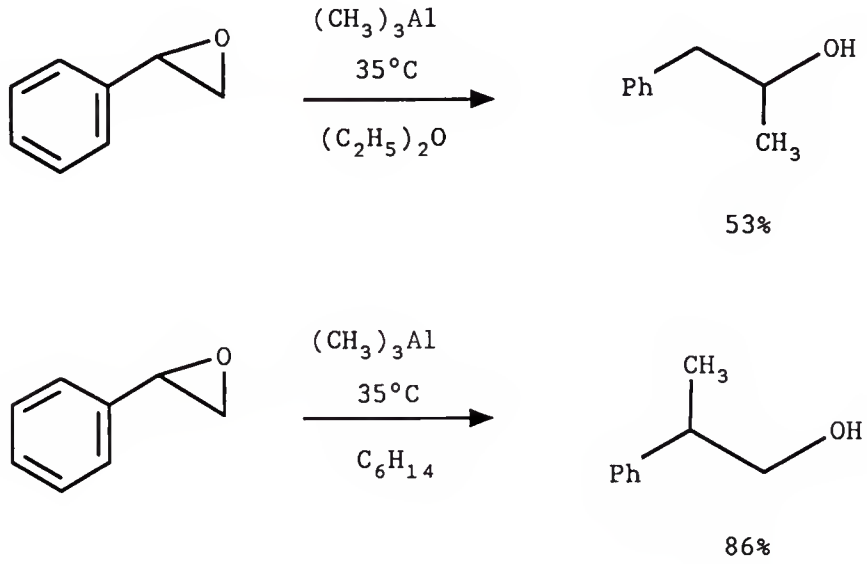


Figure 1-1

An additional illustration of the condition dependent reactions of trimethylaluminum is presented later in this work (Chapter IV).

A common nucleophilic addition to epoxides is through the malonic ester synthesis. The resulting product, a hydroxy ester, can be further manipulated enroute to a desired target molecule. A major problem associated with this approach is the rather harsh conditions necessary for the reaction to proceed, e.g. refluxing, alkaline ethanol solution. In order to alleviate this situation, a concentrated research

effort has been dedicated to the exploitation of metal mediated enolate/anion transfer reagents. Work throughout the field has been focused in the two main areas of reactivity and selectivity. Prostaglandin synthesis is itself a very active area of chemical research. It follows that a breakthrough in metal mediated anion addition could likely evolve from this field. Fried demonstrated a useful synthetic approach

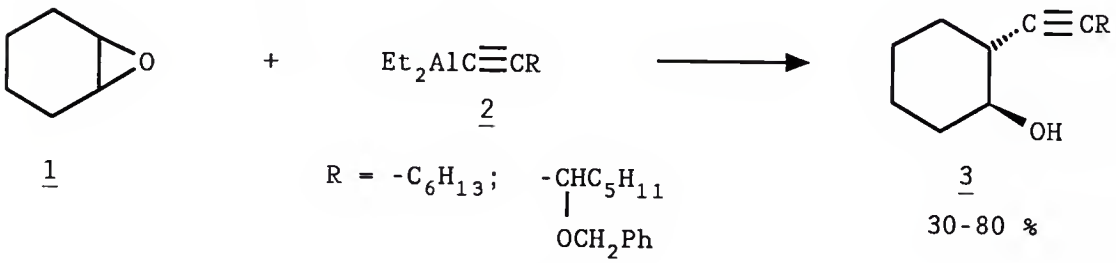
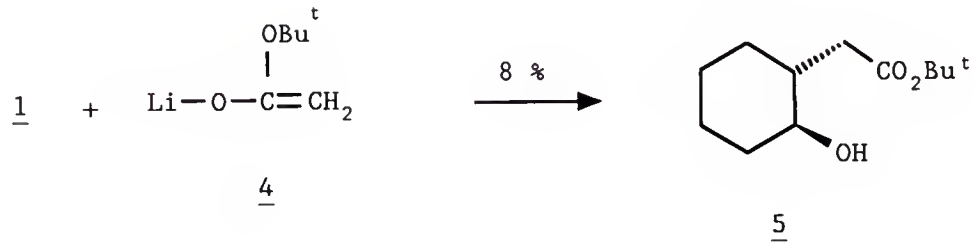


Figure 1-2

shown in Figure 1-2 involving the opening of cyclic oxiranes with various alanes while working in the area of prostaglandin synthesis.[6] These reagents were prepared in toluene by addition of diethylchloroalane (Et_2AlCl) to various lithium acetylides to give the alkynylaluminums 2. Yields of these reactions ranged from 30-80% of the anticipated *trans*-cycloalkanols.[6]

Somewhat later (1976) Danishefsky demonstrated the first examples of the reaction of an aluminum ester enolate with oxiranes.[7] This acetate equivalent was prepared in an analogous way to that of Fried's

alkynylalmuinums. Lithio *tert*-butylacetate, prepared



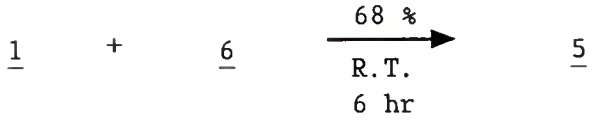


Figure 1-3

as described by Rathke,[8] on treatment with Et_2AlCl afforded the diethylcarbo-*tert*-butoxymethyl alane (Rathke alane or RkeAl) reagent as a toluene solution. The resulting aluminum enolate gave a 34% yield of the *trans*-hydroxy ester 5 when reacted with epoxycyclohexane (Figure 1-3); however, when epoxycyclohexane was reacted with the Rathke lithium salt in the absence of the Et_2AlCl, a yield of only 8% of 4 is realized. Through manipulation of the reaction temperature and time the yield of the aluminum enolate reaction was ultimately increased to

68%.[7] However, after a failed attempt at using this methodology on an oxirane in a steroidal ring system, Danishefsky discontinued investigations in this area.

This research group became involved in the area of organoaluminum chemistry in 1982 when Dr. Melean Visnick utilized the Rathke alane in the synthesis of (±)-anastrephin.[9] Visnick realized only one regio- and stereoisomer of 8 in a 24 % yield from the reaction of the Rathke alane with the vinyl epoxide shown in Figure 1-4. This reaction was carried out in toluene as were all previous examples involving the acetate equivalent. Visnick increased the yield of the reaction to 87 % by a solvent change to tetrahydrofuran (THF) after conducting a solvent study to investigate the reactivity of the reagent.[9]

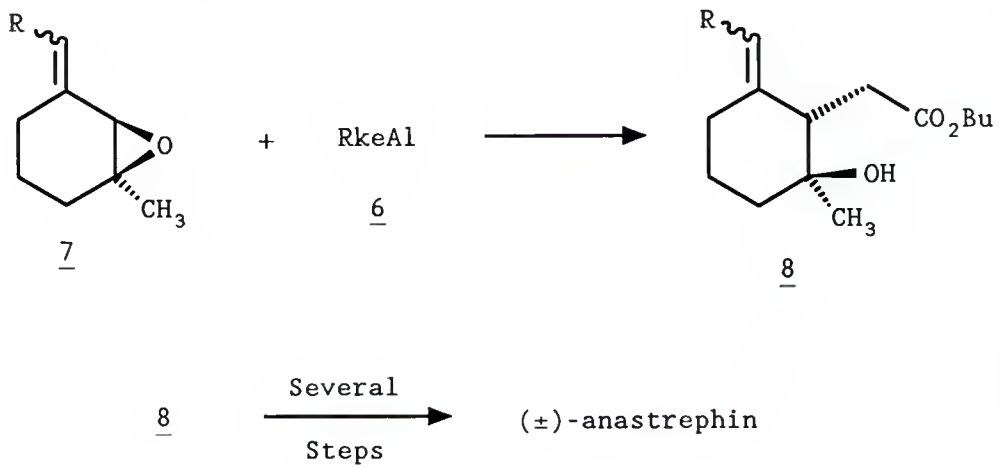


Figure 1-4

A previous investigation into the reactivity of an alkynylalane with 3,4-epoxycyclopentene showed that the solvent exerted a marked effect on the resulting product distribution (Figure 1-5).[10] A non-polar

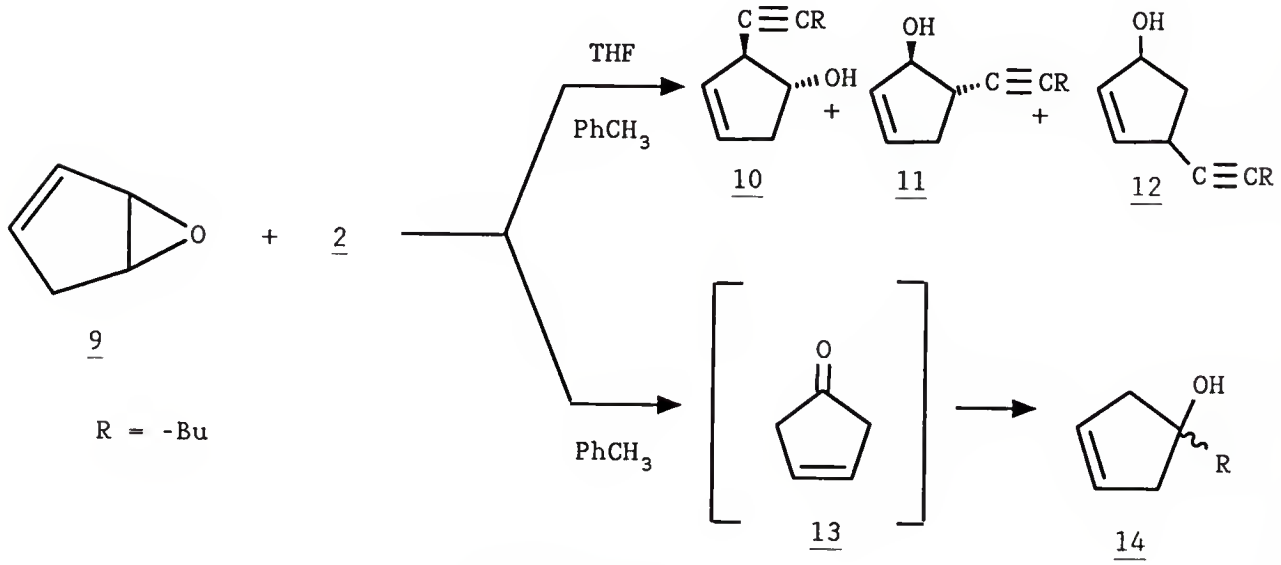
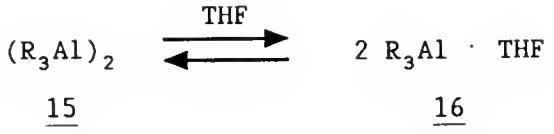


Figure 1-5

reaction medium (toluene) resulted in rearrangement of the epoxide to the enone 13 followed by the addition of the alkyne to give alcohol 14. Changing the solvent to a 1:1 mixture of toluene and THF eliminated products resulting from the rearrangement pathway. The conclusion arrived at is based on the oxophilicity of the aluminum atom. A polar solvent such as THF would satisfy the aluminum atom's oxophilicity and result in better solvation of the reagent as well as promote dissociation of the aluminum dimer (Figure 1-6). The lack of such a polar nucleophilic medium



15 16

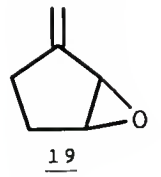
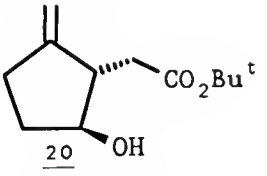
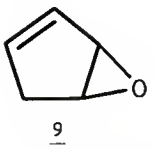
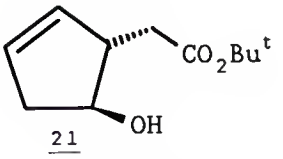
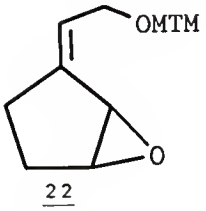
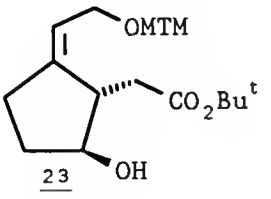
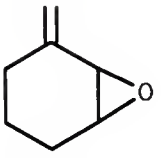
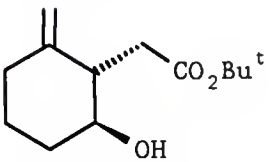
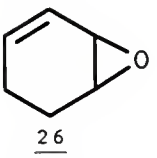
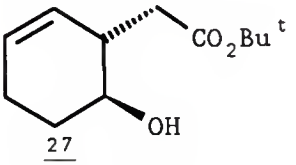
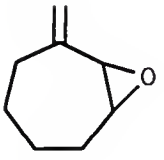
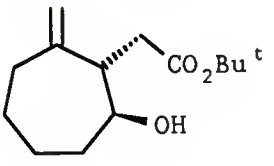
Figure 1-6

requires the reagent to become associated as dimers and larger aggregates thus reducing its nucleophilic character while not seriously affecting its catalytic activity for epoxide rearrangement. This is consistent with previous reports and applications of organoaluminums in hydrocarbon solvents such as toluene. While Visnick's solvent study on the Rathke alane echoed these results, regardless of the reaction solvent, nucleophilic attack occurred exclusively at the allylic position with no evidence of any products resulting from rearrangement of the oxirane[9].

Prompted by the favorable results obtained by Visnick, further studies were deemed necessary to investigate the scope of the Rathke alane in the ring opening reactions of α,β-unsaturated epoxides. Dr. Mapi Cuevas carried out a study designed to probe the scope, regiospecificity, and synthetic application of the Rathke alane.[11]

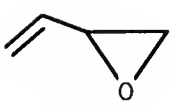
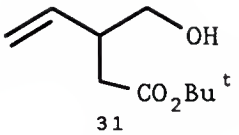
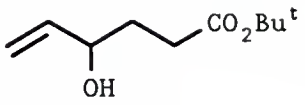
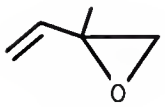
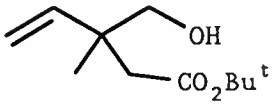
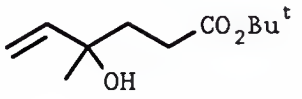
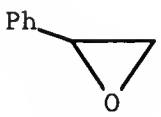
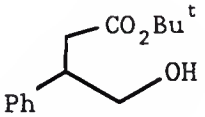
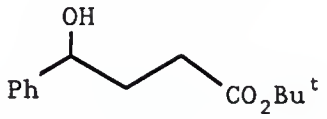
Cuevas' results on the applicability of the Rathke alane to cyclic and acyclic α,β-unsaturated oxiranes are summarized in Table 1-1 and 1-2, respectively.w As seen in Table 1-1 the 5- and

Table 1-1 Reactions of Vinyl Oxiranes with RkeAl

Oxirane	Product	Yield
 19	 20	61
 9	 21	50
 22	 23	94
 24	 25	80
 26	 27	92
 28	 29	10

6-membered cyclic vinyl oxiranes generally give good yields in their reactions with the Rathke alane while the 7-membered ring 28 gave an unexpectedly low yield. This can be explained by the locked planar geometry of

Table 1-2 RkeAl Reactions on Acyclic Vinyl Oxiranes

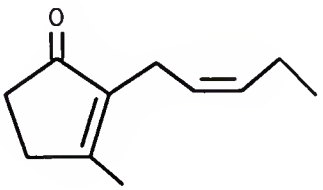
Oxirane	Products		Yield %
 30	 31	3:1  32	22
 33	 34	7:1  35	34
 36	 37	4:1  38	64

the olefin and oxirane in the smaller sized rings. The medium sized 7-membered ring 28 is inherently more conformationally flexible allowing the olefin and oxirane to exist in a non-planar relationship which reduces the stabilizing effect of the vinyl group adjacent to oxirane. This argument is further demonstrated by the poor yields and lack of regiospecificity realized with acyclic vinyl epoxides as documented in Table 1-2.

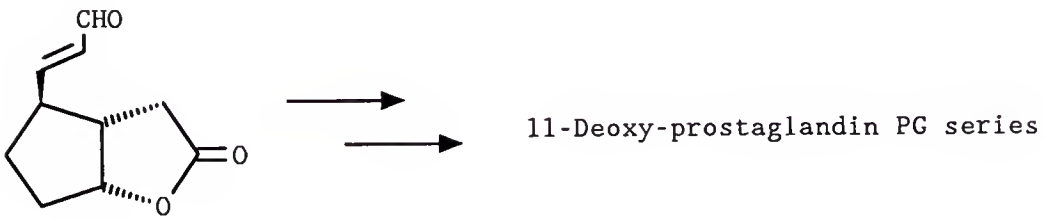
A number of experiments were carried out by Cuevas, in conjunction with this worker and others, that were aimed at determining the nature of the RkeAl

reagent. The question of the location of the metal, whether bonded to oxygen or carbon, was investigated along with the mechanism of reaction. Results of these inquiries are detailed herein and by Cuevas.[11]

In addition to the above studies, Cuevas further demonstrated the application of organoaluminum species to advanced synthetic techniques. Two formal syntheses of interesting molecules were demonstrated, that of *cis*-jasmone, 17, and an advanced intermediate, 18, (Figure 1-7) that has been



cis-Jasmone, 17



18

Figure 1-7

elaborated by Corey to prostaglandins 11-deoxy-PGE_2 and 11-deoxy-PGF_2.[11, 12]

As demonstrated above by Visnick and Cuevas the α,β-unsaturated epoxide is a very powerful starting material for the construction of a variety of natural products. The current preparation of these building blocks involves the alkaline epoxidation of cyclic α,β-unsaturated ketones followed by a Wittig olefination.[13] The preparation suffers from problems associated with the isolation of the final volatile product from the Wittig olefination reaction mixture in the final step of the sequence. Therefore, a more efficient synthesis was desired for preparation of this series of oxiranes. The first section of this dissertation will deal with the development of a new synthetic sequence for vinyl oxiranes and discuss its advantages over the previous preparations.

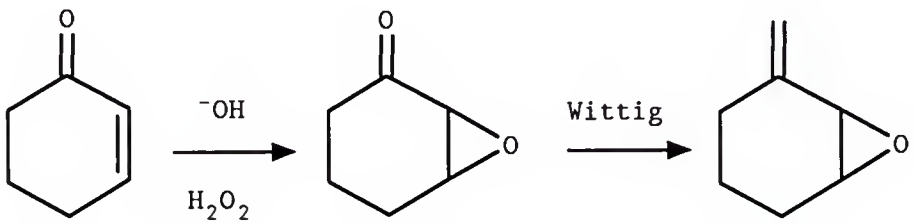
Promising more insight into the still young field of organoaluminum chemistry, additional studies were undertaken to probe the scope of the reaction of vinyl oxiranes with Rathke alane and other organoaluminum reagents with the view to provide insight into the mechanism of such reactions. In addition to the work on unsaturated epoxides, the application of the Rathke alane and structural variations of it will be demonstrated on several aldehydes and ketones. As mentioned previously, a study of the reaction of trimethyl aluminum with various ketones at elevated temperatures was undertaken as a natural outgrowth of

the above investigations. This brief study will look at the reaction and its condition dependent products in an attempt to demonstrate the utility of the reaction beyond current applications.

CHAPTER II

VINYL OXIRANE SYNTHESIS VIA THE HORNER-WITTIG OLEFINATION REACTION

As a result of an evolving study of the scope and mechanism of the highly selective ring opening reactions of vinyl oxiranes with organoaluminium reagents,[9, 11, 14] a need arose in our laboratories for the development of a convenient and efficient synthesis of the more volatile members of this series of epoxides including the cyclic exomethylene derivative 24. The standard route to the methylene



39 40 24

Figure 2-1

oxirane involves alkaline epoxidation of the respective 2-cycloalken-1-one followed by Wittig

olefination as shown if Figure 2-1.[13] While the yields associated with the epoxidation step are in the 80-90% range, the isolated yields from the olefination step were lower and often unacceptable (25-70%). The major isolation problems stem from the surprising volatility and partial miscibility with water of oxirane 24.

In an attempt to alleviate the isolation problems encountered in the current method we chose to explore an alternative pathway illustrated in Figure 2-2.

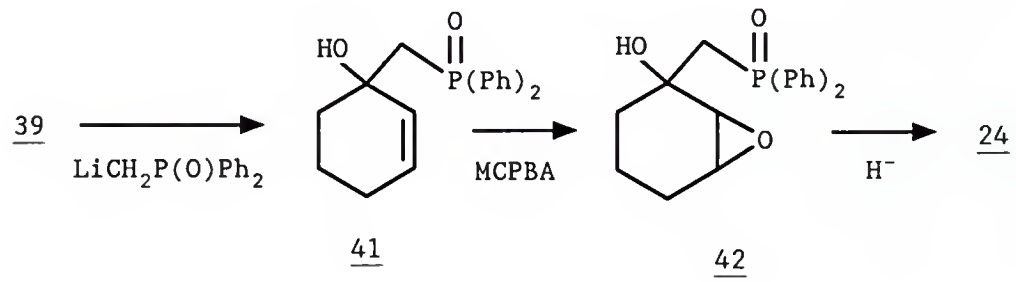
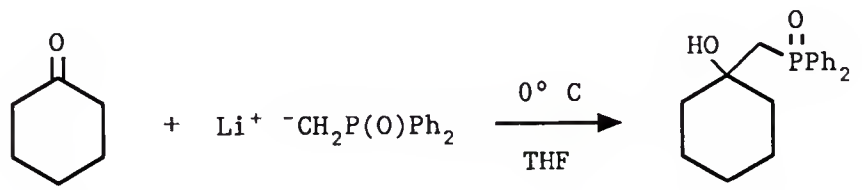


Figure 2-2

This route was suggested by the earlier investigations of Warren and coworkers on the utility of the diphenylphosphinoylethyl group in a two-step olefination procedure.[15] The initially attractive feature of this alternative scheme was the expectation of stable crystalline solids for intermediates 41 and 42. Subsequently, the methylene oxirane 24 could be generated on demand from the stockpiled epoxide 42 using potassium hydride (KH) under non-aqueous conditions and workup. Ultimately, isolation would

depend on the individual properties of the product epoxides: i) distillation directly from the reaction solvent or ii) utilization of the oxirane as a solution of the reaction solvent. Although modest in scope as a pilot approach, we were also aware of the potential synthetic bonuses of such a scheme. For example, the hydroxyl directed syn-epoxidation of the allylic alcohol 41 would, in a more substituted system, lead to an alternative diastereoselectivity not available through current means. Additionally, our method potentially offers a convenient three step protocol for the synthesis of chiral vinyl epoxides via enantioselective epoxidation of the diphenylphosphinoylmethylallylic alcohol (e.g. 41).

The first reaction attempted was the that of



43 44 45

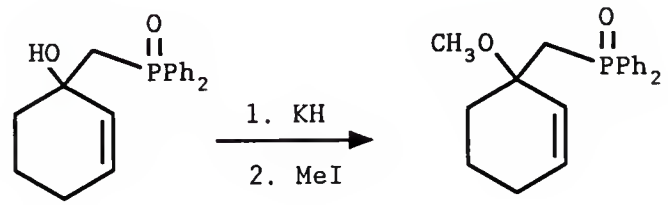
Figure 2-3

lithiomethyldiphenylphosphine oxide with cyclohexanone which resulted in the formation of a white crystalline compound that was identified as 1-(diphenylphosphinoyl)methylcyclohexanol 45 from its ^{1}H NMR spectrum (Figure 2-3).[16] Encouraged by this result,

the synthesis of the vinyl oxiranes was undertaken. Treatment of 2-cyclohexen-1-one with the lithium salt generated from methyldiphenylphosphine oxide and n-butyl lithium in THF at 0° C resulted in exclusive 1,2-addition to afford the crystalline alcohol 41 in greater than 95% yield. Öhler and Zbiral have reported the synthesis of 41 under different conditions in somewhat lower yields.[17] Epoxidation of allylic alcohol 2 with *m*-chloroperbenzoic acid (MCPBA) in methylene chloride gave excellent yields (>90%) of a crude oily epoxide mixture from which a single, crystalline epoxide was isolated as the predominant product on chromatography or trituration of the oil with pentane (94.8% yield). We tentatively assigned the *cis*-structure to this product on mechanistic grounds,[18] literature precedent,[19] and the results of a Nuclear Overhauser Effect (NOE) difference experiment. A 14 % enhancement of the C-2 methine proton signal of 42 was noted upon irradiation of the methylene protons adjacent to the phosphinoyl group. By contrast the C-2 vinyl proton for the unsaturated alcohol 41 showed a lesser enhancement of 10 %. The minor product, presumably the *trans*-isomer of 42, was not obtained in sufficient quantities for characterization.

To verify the role of the hydroxyl group in MCPBA epoxidation of 41, we next examined the epoxidation of the methyl ether 46 prepared by

O-methylation of 41 with potssium hydride (KH) and excess methyl iodide (MeI) as shown in Figure 2-4. Treatment of 46 with MCPBA yielded an intractible

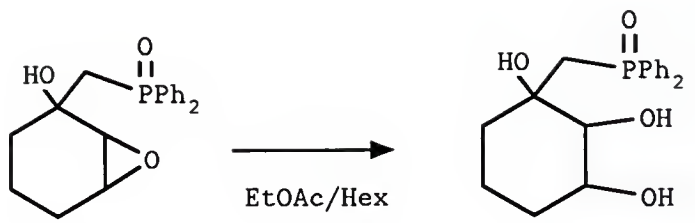


41 46

Figure 2-4

mixture of products which resisted crystallization or attempted purification. Proton and ^{13}C-NMR examination of the oil afforded evidence for two epoxides in ca. 1:1 ratio. This result is consistent with at least a significant fraction of hydroxyl directed *cis*-epoxidation for alcohol 41.

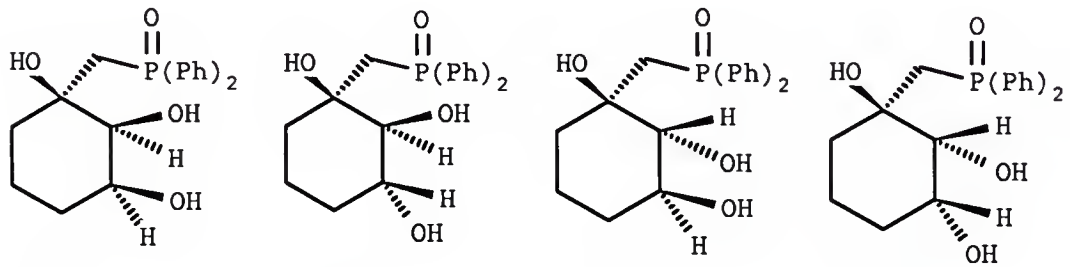
The epoxide 42 demonstrated an unexpected and surprisingly facile ring opening of the oxirane by traces of water on attempted recrystallization from an ethyl acetate-hexane (75:25) mixture to form a single crystalline compound. NMR and mass spectral examination confirmed the 1-(diphenylphosphinoyl)methyl-1,2,3-cyclohexane triol structure 47 for the homogeneous white solid deposited during the recrystallization attempt (Figure 2-5). Of the four possible diastereomeric structural candidates



42 47

Figure 2-5

for 47 (Figure 2-6), two, the *cis, cis* (48) and *trans, trans* (51) hydroxyl configurations of C-2 and C-3, can be eliminated on the basis of the proton coupling data

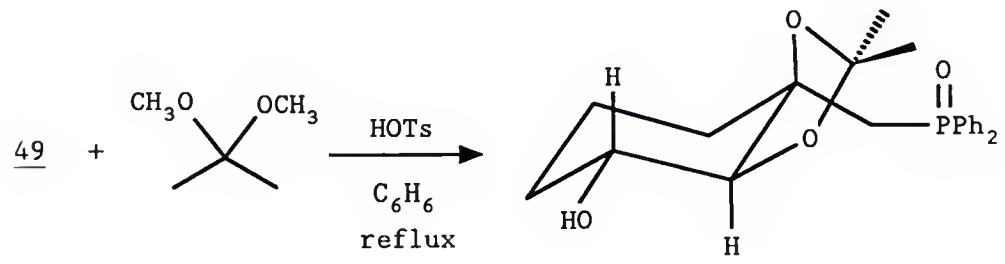


48 49 50 51

Figure 2-6

for the less shielded C-3 methine hydrogen (ddd, J = 11.50, 8.78, 4.5 Hz) which revealed two diaxial couplings. Assuming the bulky $(Ph)_2P(O)CH_2$- group is locked into the equatorial position, it is then clear the C-3 hydroxyl must also be in the equatorial position. Likewise, the C-2 hydroxyl must be equatorial in order for its methine proton (d, J =

8.77 Hz) to experience the observed diaxial coupling, thus ruling out structure 50. To confirm the assignment of structure 49 the triol was converted to its acetonide 52 (Figure 2-7) which, on NMR



52

Figure 2-7

examination, revealed the identical downfield eight line multiplet (ddd, J = 11.64, 9.06, 4.0 Hz).

Final confirmation of the structures of 41 and 42 came in the form of single-crystal X-ray examination.[20] The crystal structure obtained for 42 afforded final proof of the *cis* relationship that exists between the hydroxyl group and the oxirane oxygen as supported by the above data and discussions. Both compounds 41 and 42 exist in the half chair conformation as expected; however, the bulky diphenylphosphinoylmethyl group occupies the pseudo-axial position. Molecular models of 41 suggest that in order to accomodate hydrogen bonding the bulky diphenylphosphinoyl group assumes the pseudoaxial position to relieve severe steric crowding with the

cyclohexene ring protons. Additionally, both alcohols 41 and 42 contain an intramolecular hydrogen bond between the hydroxyl and phosphine oxide groups, in contrast to published structures of similar compounds.[21] Curiously, crystals of both 41 and 42 occupy unit cells of the same dimension.

Elimination of the diphenylphosphinoyl group from 42 was initially achieved by treatment of the epoxyalcohol with KH or sodium hydride (NaH) in N,N-dimethylformamide (DMF) at 60-65° C according to literature precedent.[15b] The desired methylene epoxide was obtained as a solution (50:50) in DMF; however, attempts to separate the volatile oxirane from DMF by vacuum distillation were unsuccessful. Due to the nature of the subsequent reactions to be carried out on the epoxides, DMF contamination was not acceptable. Therefore, a change of reaction solvent to THF was deemed advisable as subsequent organoaluminum reactions are normally carried out in THF. Treatment of 42 in THF under the above conditions afforded the epoxide as a solution containing ~25% THF as determined by ^{1}H-NMR integration.

The synthesis of the methyl substituted oxirane 56 was accomplished in a similar fashion to 24 except for a slight modification in the first step (Figure 2-8). Addition of the diphenylphosphinoyl group to 3-methylcyclohex-2-enone required lowering of the

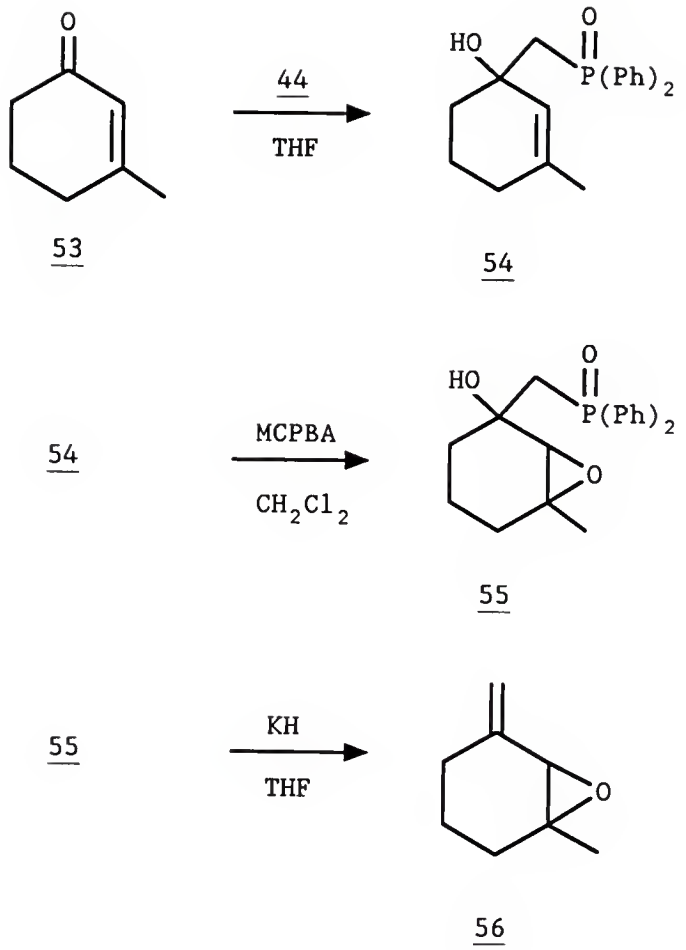
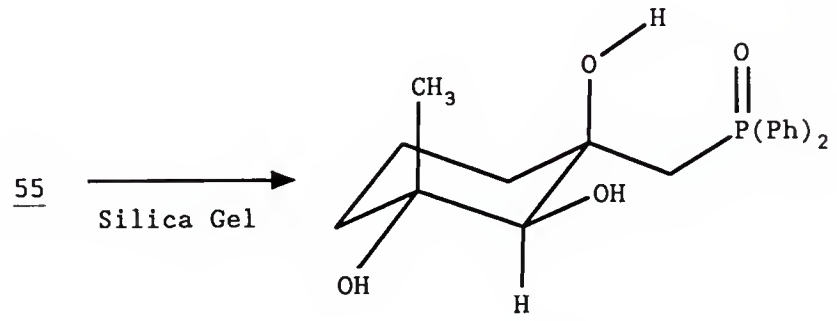


Figure 2-8

reaction temperature to -30° C in order to avoid severe side reactions that were encountered at a reaction temperature of 0° C. Operation at the lower temperature resulted in the isolation of a single crystalline solid, 54, in 97 % yield. Epoxidation with MCPBA was carried out in the same manner as that of 41 to form a single epoxide, 55, in good yields (>85 %). In an analogous fashion to 42, epoxide 55 readily opened to give the crystalline triol 57

depicted in Figure 2-9. Single-crystal X-ray analysis showed this compound to exist in the chair



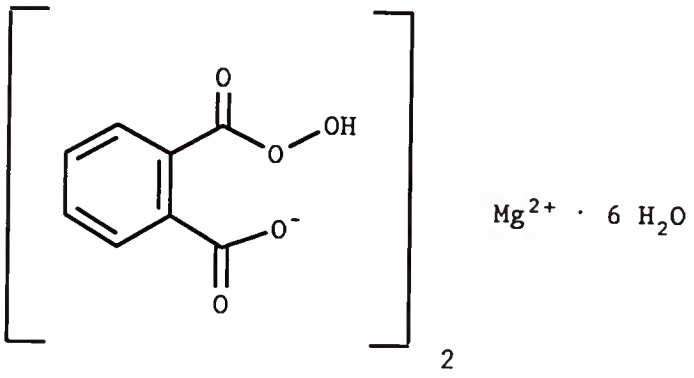
57

Figure 2-9

conformation with the bulky diphenyphosphinoylmethyl group in the equatorial position and hydrogen bonded intramolecularly to the C-1 tertiary hydroxyl group. Additionally, intermolecular hydrogen bonding involving all three hydroxyl groups exists in a network throughout the crystal lattice. The X-ray structure also demonstrates the 1,2-*cis*-3-*trans* relationship between the hydroxyl groups and the methyl group occupying an axial position. Finally, the methylene oxirane 56 was generated under the same conditions as 24, but due to its lower volatility it was isolated (65 % yield) as a pure compound by vacuum distillation through a Vigreaux column.

Further attempts were made to demonstrate the usefulness of intermediates such as 41 to different epoxidation techniques and possibly isolate the

trans-isomer of 42. The first reagent studied was magnesium monoperoxyphthalate (MMPP, Figure 2-10).



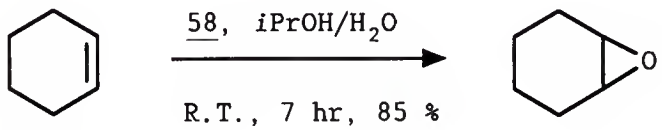
58

Figure 2-10

This reagent is marketed as a replacement for the commercial grade of MCPBA (80-85 %) that is no longer available due to hazards associated with its preparation. MCPBA is now available in only a 50-55 % grade from the chemical supply houses. MMPP is sold as its hydrated salt containing 80 % of the active oxidant. Successful oxidations of several different substrates and systems have been accomplished with MMPP and it was shown to be a suitable replacement for MCPBA.[22] Oxidations carried out with MMPP are normally run in halogenated or alcoholic solvents under phase transfer catalysis (PTC) conditions. Reactions with MMPP were run on the methyl ether 46 and 2-cyclohexenol. The reaction of 46 was carried out in two-phase methylene chloride/water solution

under (PTC) conditions with *tert*-butylammonium bromide at 0° C. Monitoring of the reaction by thin layer chromatography (TLC) revealed no product formation after 20 hr of stirring so the reaction was warmed slowly to reflux. A product more polar than the starting material was detected in a small amount by TLC. Preparatory TLC was used in an attepmt to isolate this new compound; however,liberation of the compound from the silica media was not possible, indicating an extremely polar species or one that is difficultly soluble such as the triol 49. If any of the epoxide did form it would follow that it further reacted to open the oxirane to the diol.

The reaction of MMPP with cyclohex-2-enol was carried out at room temperature in *iso*-propanol under PTC conditions. Previous reports have demonstrated the epoxidation of cyclohexene under similar conditions in 85 % yield after 7hr (Figure 2-11).[22]

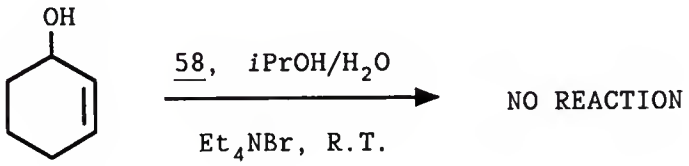


59 1

Figure 2-11

This precedent would predict that the reaction of MMPP with 2-cyclohexenol would afford the epoxy alcohol in good yield. After stirring for 17 hr at room

temperature resulted in no reaction, the solution was warmed to reflux for an additional 2 hr with no effect on the progress of the reaction (Figure 2-12). Further literature search revealed no previous examples, successful or otherwise, demonstrating the



60

Figure 2-12

utility of MMPP on allylic alcohols. One well known technique for the epoxidation of allylic alcohols is the Sharpless reaction.

The metal-catalyzed epoxidation by *tert*-butylhydroperoxide was first reported as a useful synthetic tool for the epoxidation of olefinic alcohols in 1973.[19] Since this time much work has been dedicated to expanding the scope and enantioselectivity of the now so-called "Sharpless epoxidation." Success of this epoxidation reaction would then open up the possibility of achieving the stereoselective oxidation of chiral olefins through the use of tartrate esters in the reaction medium.[23]

Figure 2-13 illustrates one example noted in the original communication of the procedure by Sharpless

which was the oxidation of 2-cyclohexenol by *tert*-butylhydroperoxide in refluxing benzene in the presence of a vanadium catalyst (vanadyl acetyl acetonate, $VO(acac)_2$) which resulted in very good yields and excellent isomeric purity (98 % *syn* addition). Unfortunately, our product epoxide 42

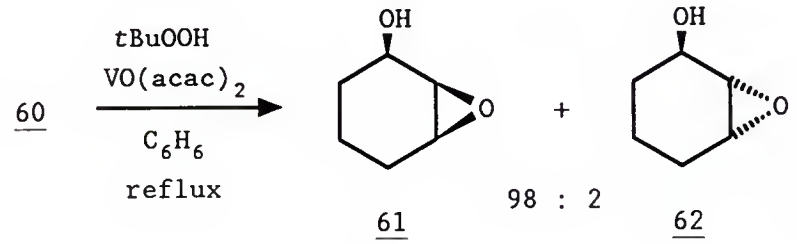
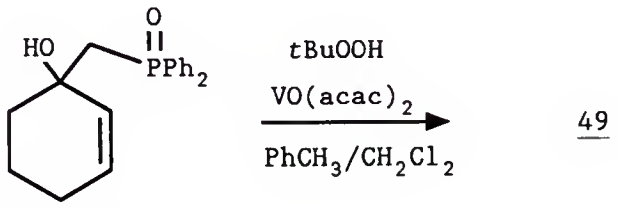


Figure 2-13

would not survive under such harsh conditions due to its facile ring opening to the triol 49. A later review by Sharpless and Verhoeven on these oxidation reactions noted that the heating of reactions catalyzed by vanadium was unnecessary and, in fact, "proceed readily at, or below, room temperature."[24] Encouraged by this, a room temperature solution of 41 in methylene chloride was subjected to a toluene solution of *tert*-butylhydroperoxide in the presence of $VO(acac)_2$ catalyst. The reaction was checked by TLC after 5 hr to show product formation along with unreacted starting material. No notable change after an additional 15 hr of stirring prompted the addition of a second equivalent of the oxidizing agent.

Continued stirring for a further 48 hr resulted in the consumption of all starting olefin and a reduction in the R_f value of the product. Workup was carried out as described in the original literature and the



42

Figure 2-14

product was isolated as a yellow-tinted solid that precipitated upon washing with water. Spectral investigation by ^1H NMR showed this compound to be the ring opened epoxide 49 (Figure 2-14). Apparently, 42 is extremely sensitive to any sort of acid present in the reaction solution or in the reaction workup. The success found in the MCPBA oxidation must be contingent on the buffering effect of the sodium bicarbonate present in the reaction mixture.

A further example of the possible synthetic uses of compounds similar to 41 and 54 is demonstrated by their ability to undergo both O- and C-alkylation. The O-alkylation was demostrated in the formation of the methyl ether 46 shown above in Figure 2-4. The ability to be alkylated on the carbon *alpha* to the phosphinoyl group was noted in an attempted

preparation of 46. Upon generation of the anion of 41 with BuLi at 0° C a deep red solution resulted when a slight excess of base was added. Quenching of this reaction mixture with excess MeI resulted in the isolation of a mixture of the O- and C-alkylated products and recovered starting material. Subsequent generation of the dianion with BuLi and quenching with MeI afforded two diastereomers (3:1 ratio) of the C-alkylation product in good yield (86 %) with no O-alkylation product observed (Figure 2-15). The

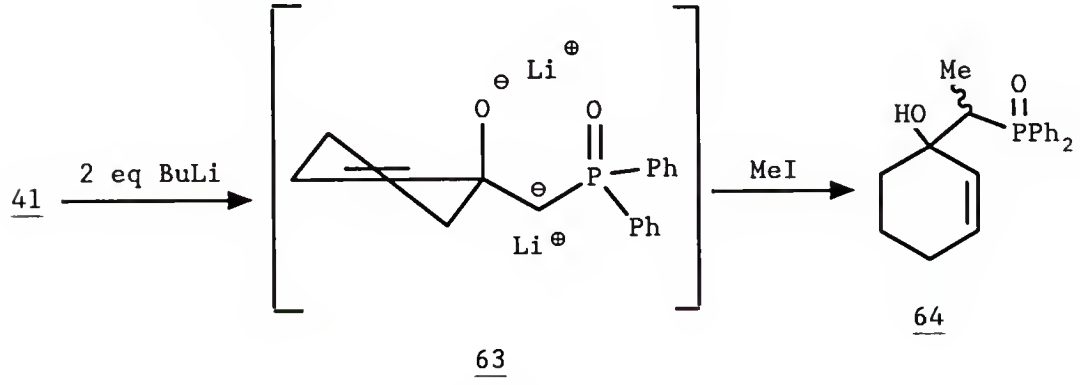


Figure 2-15

resultant C-alkylation product can be subjected to conditions necessary for elimination of the phosphorous group to yield the ethylidene sidechain. The yield and ratio of these E- and Z-alkenes could be of synthetic interest.

Warren has demonstrated the use of lithioethyl-diphenylphosphine oxide on benzaldehyde in the selective synthesis of Z-1-phenylpropene following the

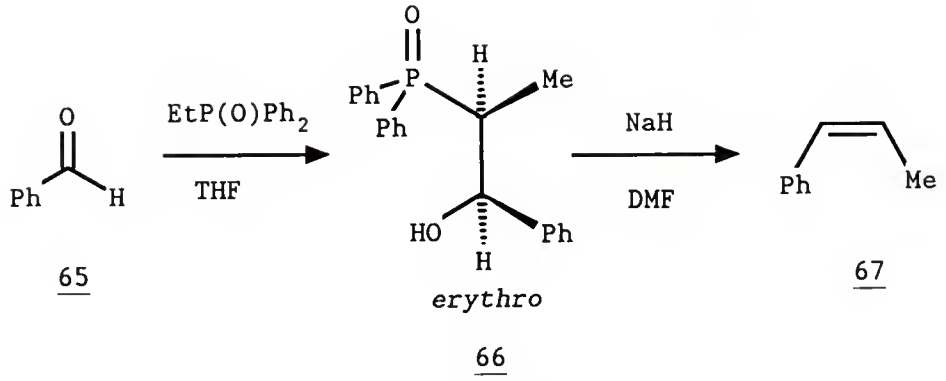


Figure 2-16

elimination of the diphenylphosphinoyl group as shown in Figure 2-16.[15b] The initial addition to the aldehyde results in the formation of the *erythro* isomer (1RS, 2SR) as the major product, 78 %, which upon elimination of the diphenylphosphinoyl group affords the Z-alkene in 75 % yield. The E-alkene is accessible via oxidation of the isomeric alcohols to the ketone, followed by the sodium borohydride ($NaBH_4$) reduction to primarily the *threo* isomer (89 % of the mixture), which gives the E-alkene upon elimination. An investigation was undertaken to obtain the *threo* isomer in a more direct route, thereby providing a complimentary method to Warren's Z-alkene synthesis.

Benzaldehyde was subjected to lithiomethyl-diphenyphosphine oxide in THF at -78° C and allowed to warm to room temperature to yield the anticipated addition product (Figure 2-17).[25] Treatment of the substituted ethanol with 2.0 eq of BuLi resulted in

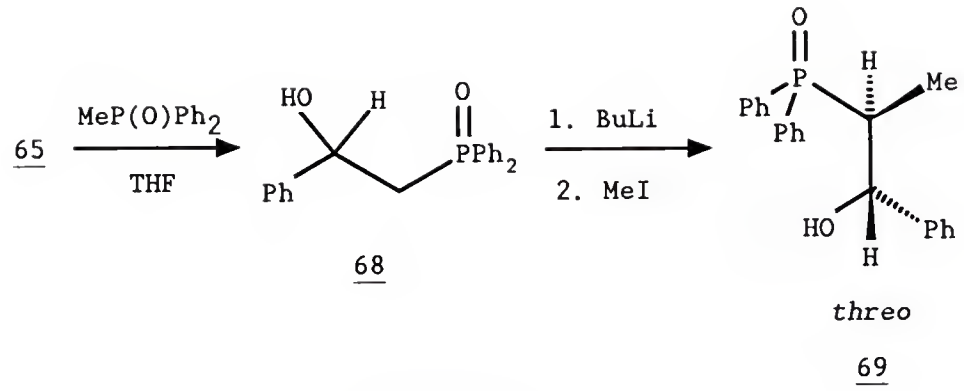


Figure 2-17

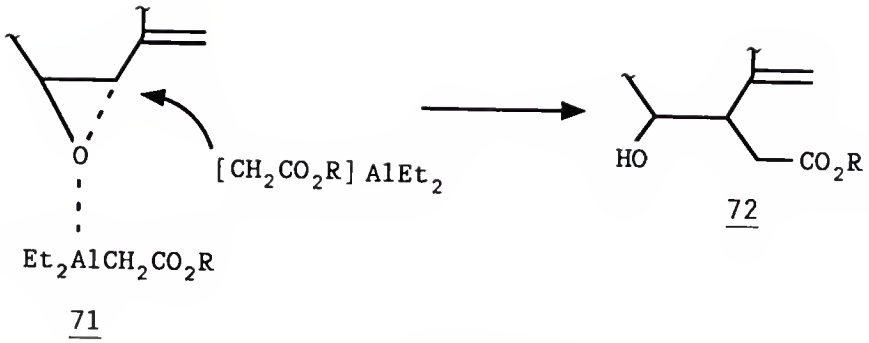
the formation of the dianion which was quenched by the addition of excess MeI. Spectral examination of the crude reaction mixture revealed two diastereomers present in a ratio of approximately 5:1. Separation of these isomers by flash column chromatography resulted in the isolation of the major component as a pure compound that ^{1}H NMR confirmed to be the *threo* isomer as assigned by Warren.[15b] The minor component was not obtained in sufficient quantities from the chromatography for accurate characterization; however, the peaks present in the ^{1}H NMR of the mixture belonging to the minor isomer are in good agreement with those published for the *erythro* isomer.[15b] The method described herein allows isolation of the intermediate alcohol responsible for the complimentary alkene to that of the Warren method. This success has spawned continued work in the area of alkylphosphinoyl addition to carbonyl compounds and subsequent

alkylation *alpha* to the phosphine oxide and its application to natural product synthesis.[26]

CHAPTER III

STRUCTURE AND REACTIVITY OF ALUMINUM ENOLATES

The earliest examples of aluminum mediated anions in oxirane ring opening reactions employed for the synthesis of prostaglandins reported the use of the alane species in an 8.5 molar excess.[6] Danishefsky's report of the initial success of the Rathke alane noted a 2.5 molar excess ot the organometal.[7] Likewise, Visnick found the optimal stoichiometry to be a 2.3 molar excess of the Rathke alane in reactions with vinyl oxiranes.[9] The work described by Cuevas with the Rathke alane on cyclic and acyclic α,β-unsaturated epoxides was accomplished with a working stoichiometry of a 2.5-3.0 molar alanyl excess.[11] With the general acceptance of a necessity of 2.0 equivalents of the organoaluminum species a simple mechanism of coordination to the oxirane by one equivalent and subsequent delivery of the anion by a second equivalent may be proposed as shown in Figure 3-1.

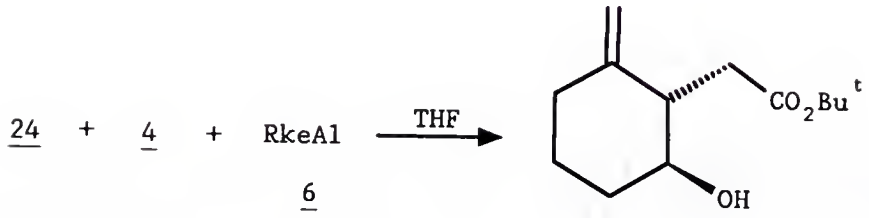


71 72

Figure 3-1

In the case of the vinyl oxiranes this could explain the regiospecificity demonstrated in attack at the allylic site due to stabilization of the charge build up upon weakening of the carbon-oxygen bond. A mechanism of this sort would allow for the reaction to proceed with a single equivalent of the enolate and a catalytic excess of the Lewis acid (Et_2AlCl). A series of experiments were undertaken to test this assumption and determine the necessary stoichiometry of the reaction. The three key reactions investigated subjected 3-methylene-1,2-oxidocyclohexane, 24, to varying amounts of the Rathke alane; the results of these reactions are collected in Table 3-1. The standard reaction was carried out with 3.0 equivalents of the Rathke alane 6 to determine the yield under established conditions. Thereafter the remaining reactions utilized 1.5 equivalents of the alane 6. A final attempt to establish a cooperative competition

Table 3-1 Stoichiometric Studies on RkeAl

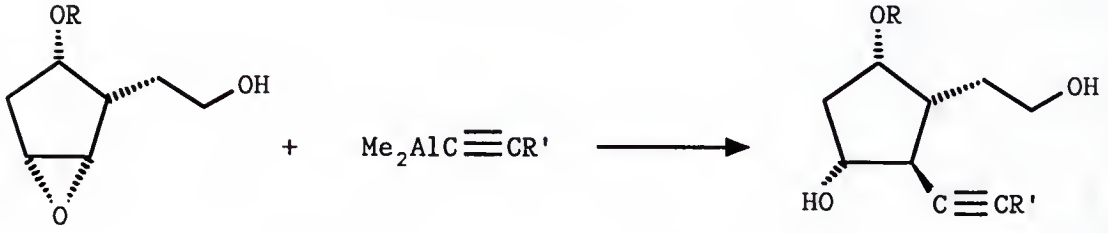


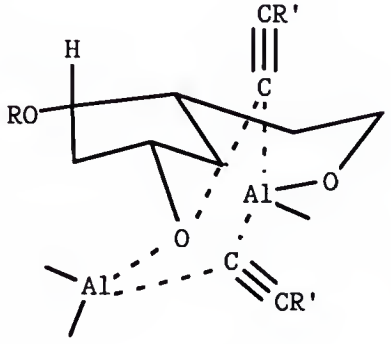
Rxn	6 (eq)	4 (eq)	Yield (%)
1	3.0	0	75
2	1.5	0	48
3	1.5	1.5	3.4

reaction between the Rathke alane (6, 1.5 eq) and the Rathke lithium enolate (4, 1.5 eq) was examined to determine if the reaction is indeed catalyzed by the aluminum species. The results of these experiments (Table 3-1) clearly support the need for more than a single equivalent of the aluminum species in order for the reaction to proceed with good yields and dismiss the assertion that the aluminum is only acting in a catalytic fashion. In view of the observed requirement for at least two equivalents of the alane species one might envisage a dimeric species as the reactive intermediate.

In fact Fried[6a] has proposed a mechanism involving an alane dimer derived 6-membered ring

transition state in the reaction of alkynylalanes with epoxides to form the *trans* substituted alcohols as shown in Figure 3-2. It would follow that the Rathke

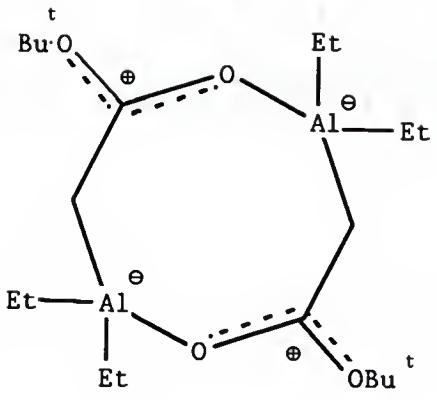




73

Figure 3-2

alane could react in an analogous fashion with the vinyl oxiranes through a hemi ring-opened 8-membered dimer as shown in Figure 3-3. The suggested mechanism for addition as depicted in Figure 3-4 begins with the coordination of the oxirane oxygen to the aluminum and subsequent rupture of the dimer 74. Displacement of the THF ligand by the oxiranyl oxygen results in formation of a reactive complex in which oxiranyl coordination to the metal weakens the allylic



74

Figure 3-3

carbon-oxygen bond thereby increasing the positive character of the allylic carbon. This electron deficient carbon is then attacked by the reverse end of the opened dimer 74 which then delivers the enolate moiety. One may view this mechanism in colloquial terms as the "ice-tong" mechanism. In view of the postulation of a dimeric structure for the RkeAl, an investigation into its structure in solution was deemed necessary.

A sample of the Rathke alane was prepared in the usual manner as described in the experimental section. Neat dimethylaluminum chloride rather than the hexane solution of the Et_2AlCl was used in an attempt to aide in the simplification and interpretation of the NMR spectra. The reagent solution was warmed to 0° C and the solvents removed in vacuo to give the aluminum

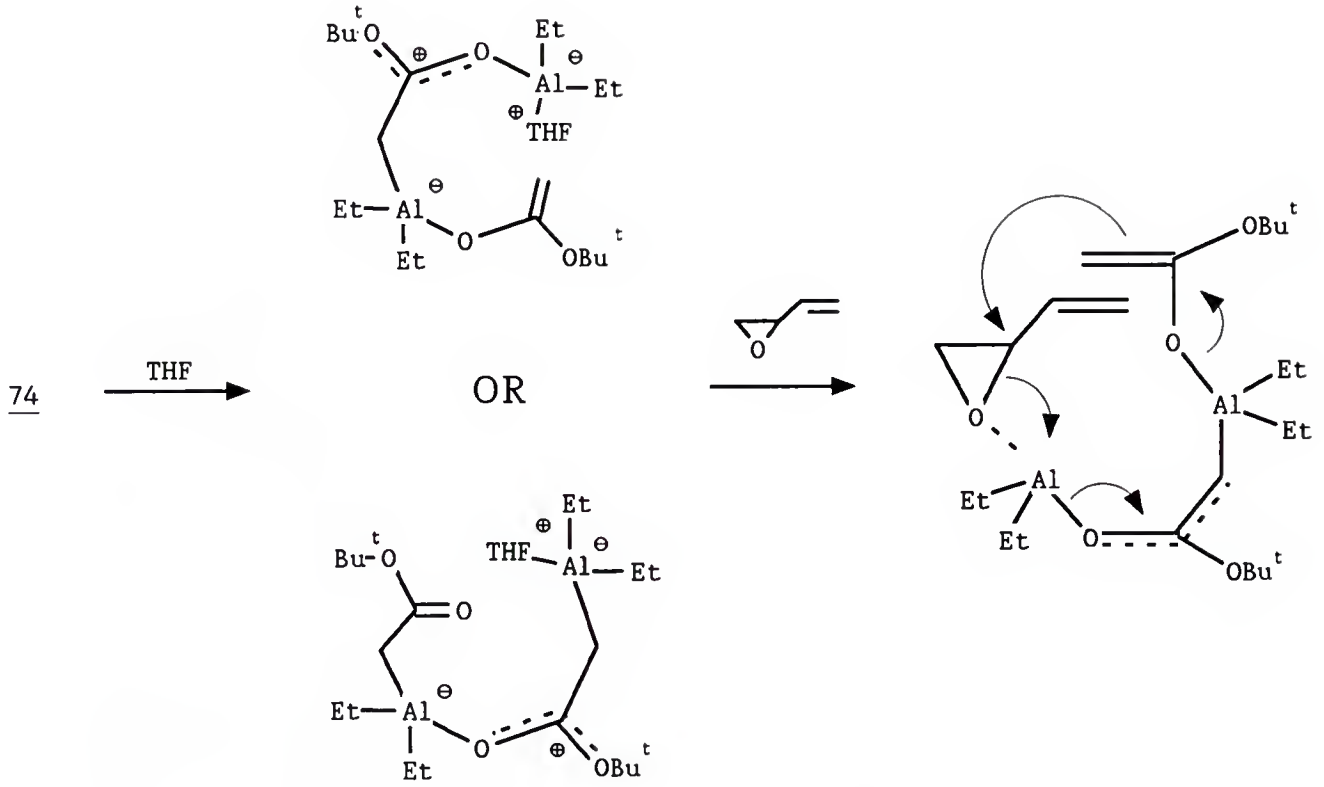
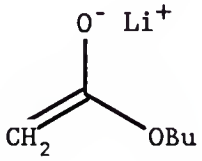


Figure 3-4

salt which was then dissolved in THF-d_8 and cooled to -78° C. The resulting spectra, recorded at various temperatures, were sufficiently complex to indicate the presence of more than one species or perhaps unsymetrical dimers or oligomers.[27] The absence of signals in the vinylic region of the ^1H NMR would suggest the lack of a true enolate structure similar to that reported by Rathke for the lithium salt of *tert*-butyl acetate.[8] Spectral evidence obtained on the lithium salt in benzene-d_6 included two doublets at 3.14 and 3.44 ppm and the absence of a signal in the IR spectrum between 1650 and 2000 cm^{-1} corresponding to a carbonyl stretch. Figure 3-5 illustrates the enolate structure of 4 supportive of this evidence.

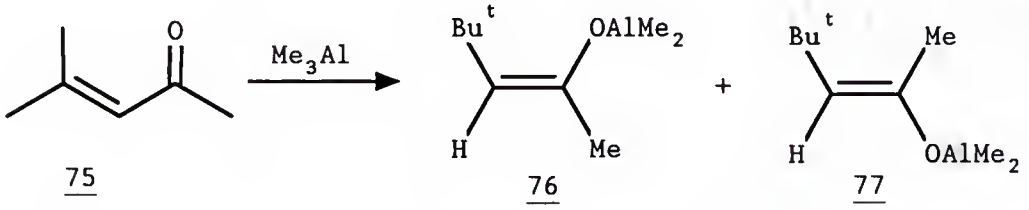


4

Figure 3-5

Researchers in the area of aluminum enolates have depicted many different structures for these species without citing experimental data or literature precedent. Japanese workers have used aluminum

enolates in aldol condensation reactions where they depict an O-metallated species with no substantiating evidence.[28] Mole and coworkers have reported the

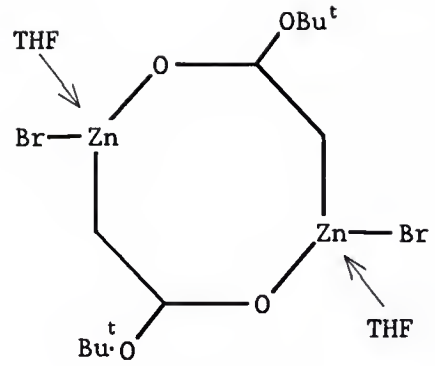


75 76 77

Figure 3-6

isolation and characterization of the Z- (76) and E-enolates (77) shown in Figure 3-6 from the reaction of trimethylaluminum on mesityl oxide.[29] Further investigations revealed that the Z-enolate 76 existed in the dimeric form and the E-enolate 77 was made up of dimers and trimers. The lack of a monomeric species in this study encouraged us with respect to our proposal of the dimeric nature of the Rathke alane; however, the exact structure of the dimer was still in question.

A report on the X-ray diffraction study of the Reformatsky reagent generated from *tert*-butyl bromoacetate was published in 1983. The structure arrived at by the workers was that of a dimeric species with each metal atom in the environment of two oxygens, a bromine, and a carbon atom (Figure 3-7).[30]

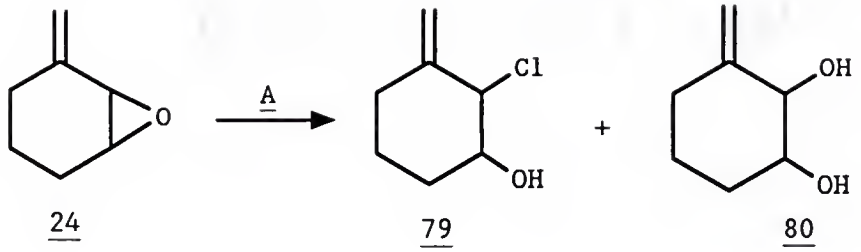


78

Figure 3-7

All of the bonds in the non-planar species are of typical single bond lengths. With this information on hand we have greater confidence in the suggestion of the dimeric species 74 for the Rathke alane and the associated reaction mechanism shown in Figures 3-3 and 3-4, respectively.

Side products observed in these aluminum enolate reactions include the self-condensation products of the ester enolate and chlorohydrin and glycol formation. In carrying out reactions with the Rathke alane it is imperative that all reagents are dried prior to use; otherwise, any water present in the system will quench the enolate and subject the starting material to the unreacted Et_2AlCl resulting in the formation of the ring opened products as shown in Figure 3-8. Intentional treatment of the vinyl



24 79 80

A	
Et_2AlCl	1 : 2.1
HCl/ice	1.6 : 1

Figure 3-8

oxirane with the chloroalane resulted in formation of 79 and 80 in a ratio of 2.1:1 in favor of the glycol. Subjecting the starting oxirane to the standard workup conditions (10% HCl and ice) afforded the same two compounds to a lesser extent in a ratio of 1.6:1 in favor of the 1,2-halohydrin. The presence of glycol 80 could lead one to suggest it originates from unreacted starting oxirane; though this can not be ruled out, one must also consider the possibility of it being generated upon hydrolysis of the chlorohydrin 79.

The reactions of the Rathke alane with carbonyl compounds follow a different course. Rathke's lithium salt will react with aldehydes and ketones to give the hydroxy esters.[8] In our hands 1.2 equivalents of the lithium salt resulted in only 38.5% conversion of

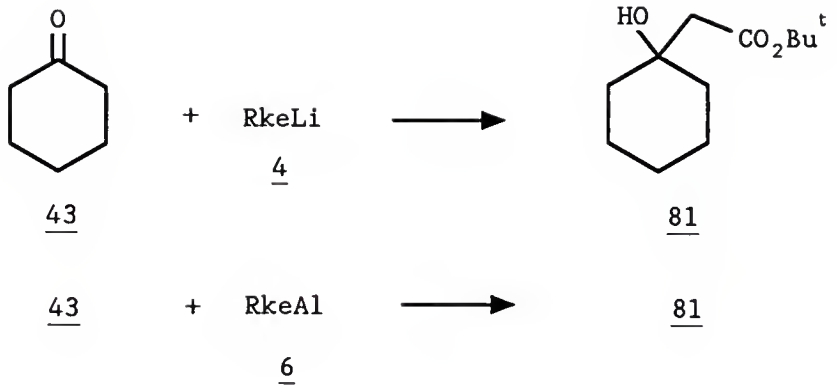


Figure 3-9

cyclohexanone to 81 after 20 min at -60° C whereas 1.2 equivalents of the Rathke alane afforded 76.7% of the adduct after 30 min under the same conditions (Figure 3-9). In this instance the aluminum may be acting as a catalyst and activating the carbonyl group for addition through a 4 membered transition state, Figure 3-10.

Several *para*-substituted benzaldehydes were subjected to 1.2 equivalents of the Rathke alane in the presence of 0.4 equivalent excess Et_2AlCl in THF at -60° C (Figure 3-11). The various substituents were chosen to determine if the rate of the addition reaction was dependent on any electronic factors in the molecule. All of the aldehydes studied resulted in similar yields of 60-70% with the reaction being essentially complete in under 10 min.

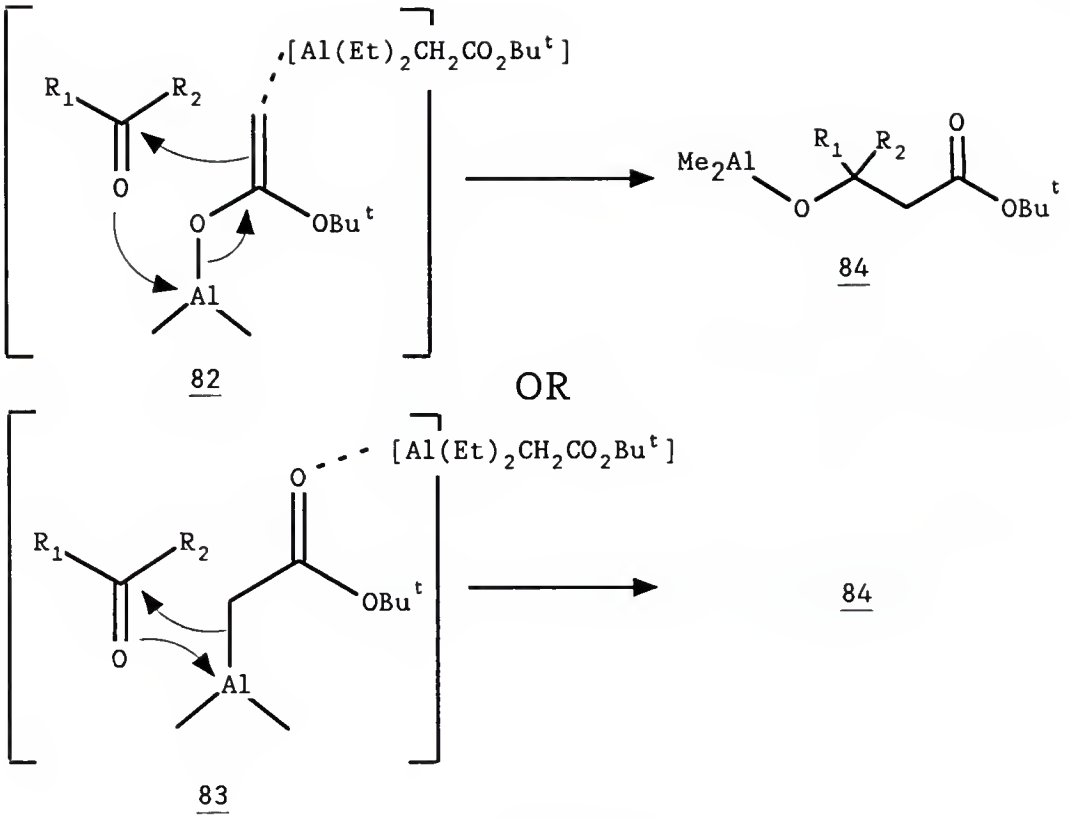
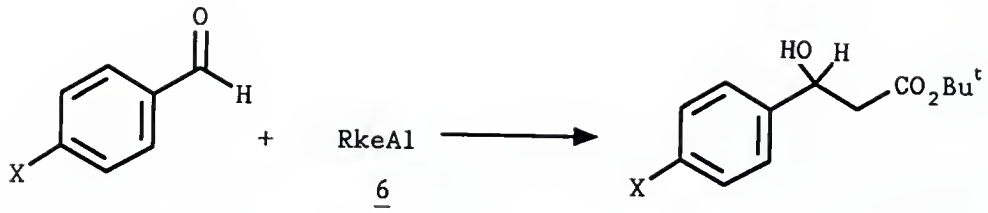


Figure 3-10

Explorations into variations of the enolate 6 to expand its utility for the synthetic chemist was the next logical step in these studies. The first change was from an acetate to a propionate equivalent in the form of the *tert*-butylpropionate. The aluminum propionate enolate (MeRkeAl, 95) was prepared in the same fashion as the Rathke alane and used in the same stoichiometric proportions. The reaction of the MeRkeAl 95 with 3-methylene-1,2-oxidocyclohexane resulted in the expected addition products (Figure



X = H; 85
CH_3; 87
OCH_3; 89
Cl; 91
NO_2; 93

X = H; 86
CH_3; 88
OCH_3; 90
Cl; 92
NO_2; 94

Figure 3-11

3-12). The goal of obtaining a diastereoselective addition was not realized as a 68% yield of 96 was obtained in a 1.2:1 ratio of isomers.

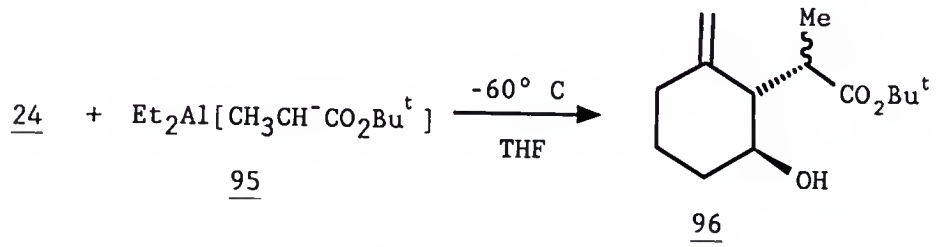
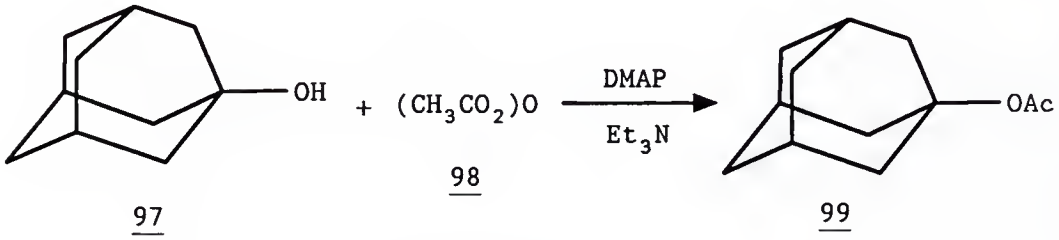


Figure 3-12

An interesting and quite possibly more synthetically useful adaptation of the enolate may be found in the variation of the alcohol portion of the alanyl ester. Thus acetylation of a chiral alcohol or one having sufficient bulk to induce severe steric bias could result in the formation and isolation of

predominantly one stereoisomer (diastereomer or enantiomer) from the Rathke type reactions. The bulky

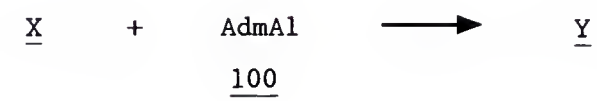


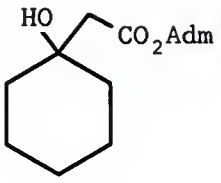
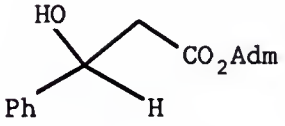
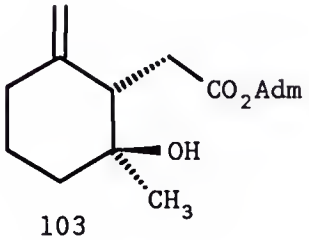
97 98 99

Figure 3-13

adamantyl group in 1-Adamantyl acetate, prepared from 1-adamantanol and acetic anhydride as shown in Figure 3-13,was examined as a steric biasing agent to help induce stereoselectivity during acetate delivery. A second consideration was the identification of the products by GC/MS through a parent mass peak that is not present in the *tert*-butyl ester due to facile loss of the *tert*-buty group as isobutylene or as C_4H_9O. The aluminum enolate (AdmAl, 100) was generated analogously to RkeAl and its reactions were run under the standard Rathke alane conditions with various functionalities (Table 3-2). The yield of the β- and γ-hydroxy esters were good to modest with the exception of styrene oxide (36). Unfortunately, upon analysis of the reaction mixture by GC/MS, no parent mass peak was realized due to the facile loss of the adamantyl cation; therefore, without further

Table 3-2 Reactions of Adamantyl Acetate Alane with Carbonyl Compounds and Oxiranes



X	Y
43	 101
85	 102
56	 103
36	Intractable Solid

purification the esters were hydrolyzed to their respective carboxylic acids for characterization.

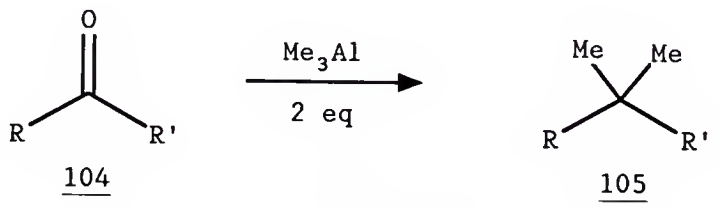
The reaction of the AdmAl with styrene oxide failed to give any addition products even after

extended reaction times and warming to room temperature. Reaction mixture analysis by capillary GC revealed peaks attributable to the styrene oxide, 1-adamantyl acetate, and 1-adamantanol. The presence of the adamantanol indicates that some form of reaction has taken place in order to liberate it from the ester. Continued monitoring of the reaction via GC showed a steady decline in the styrene oxide signal and growth of the alcohol signal; however, no response was detected for any sort of addition product leading us to believe that the aluminum species facilitated polymerization of the epoxide to a nonvolatile species. This was surprising owing to the fact that styrene oxide reacts with the Rathke alane in a 64 % yield to form the two isomeric addition products in a 4:1 ratio favoring attack at the benzylic site.[11]

CHAPTER IV

ALKENE FORMATION VIA TRIMETHYLALUMINUM ACTION ON KETONES

The reactions involving alkylaluminum compounds with carbonyl compounds are well documented,[31, 32] and some of these reactions and their anomalies were described in Chapter I. In particular, Mole has demonstrated the ability of trimethylaluminum (Me_3Al)



104 105

Figure 4-1

to act as an exhaustive methylating agent in the presence of tertiary or benzylic alcohols and an assortment of ketones (Figure 4-1).[33, 34] Prior to this, no method existed for the direct exhaustive methylation of carbonyl compounds. Yields of the *gem*-dimethylation product in the work reported by Mole range from 30% to complete conversion. The reactions were carried out with a 2-3 mole excess of Me_3Al in a

sealed reaction vessel under various solvent, temperature and reaction time conditions. A three-step pathway for this reaction has been proposed by Mole as shown in Figure 4-2. A persistent side

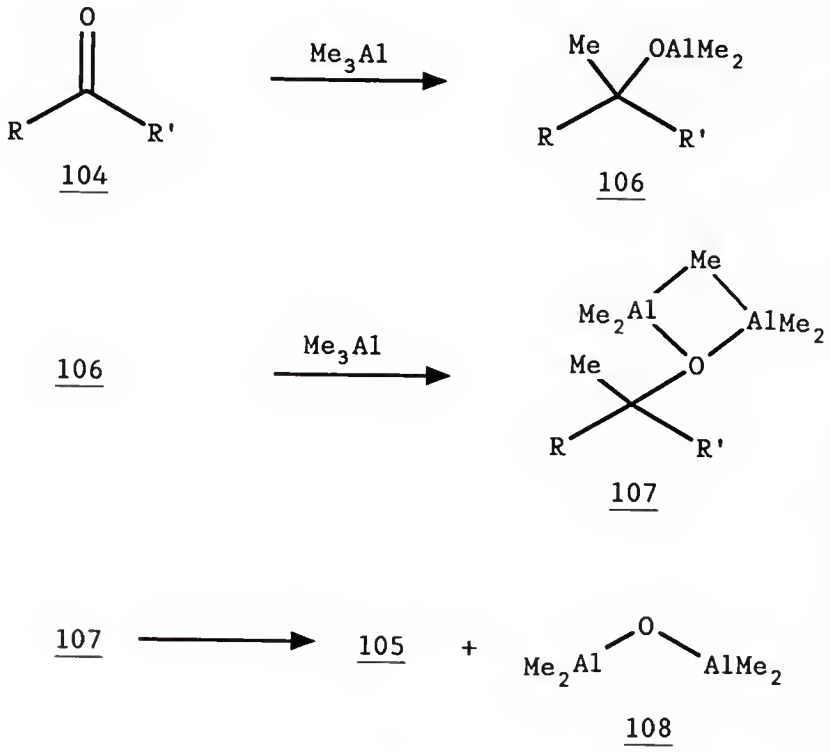
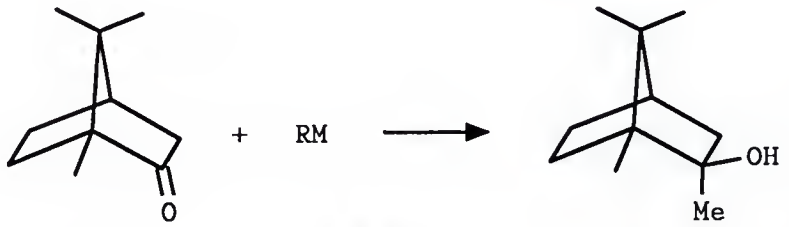


Figure 4-2

reaction noted in many of the examples investigated by Mole is alkene formation which is believed to result from elimination after initial methyl addition.[34] The contribution of alkene formation to the product distribution ranges from a trace amount to as much as 50%, the major component. Herein we report conditions that allow the isolation of alkenes as the predominant, if not sole, reaction product.

Entry into this area of research was gained through an attempted methylation of (+)-*d*-camphor, 109, as illustrated in Figure 4-3, to obtain the tertiary alcohol 110 for use as a chiral auxilliary in



109 R = Me 110

M = metal

Figure 4-3

the Rathke alane investigations. Initial attempts at peparation of the desired alcohol through the traditional means of a Grignard (MeMgBr) reaction or addition of methyl lithium gave less than satisfactory yields of ~50% conversion to 110. Starting ketone was always recovered despite the use of a large excess of the organometallic reagent. Treatment of camphor with excess trimethylaluminum in refluxing hexane resulted in a ~60% conversion to the carbinol 110 after 40 hours. Still, considerable camphor was recovered from this reaction. Alternatively, a somewhat greater yield of ~70% was realized upon subjecting the camphor to excess Me_3Al in refluxing toluene for 5.5 hr. The most profitable conditions discovered depend on

pretreatment of an ethereal solution of ketone 109 with Me_3Al (2.0 eq, 1 hr) followed by MeMgBr (5.0 eq, 3.5 days) which resulted in an ~80% transformation to 110. The question remained as to whether the two organometals react to form an alanate (R_4Al^-) as the active methylating agent or if the Me_3Al acts in the capacity of a Lewis acid and activates the carbonyl toward nucleophilic addition. A subsequent search of the literature uncovered similar results using $LiAlMe_4$ in an ether solution as reported by Ashby's group in 1974.[35] Our attempts to carry out the $LiAlMe_4$ reaction in toluene resulted in no reaction even after prolonged heating, further demonstrating the effect of solvation on organoaluminum reagents. When the reaction of Me_3Al in toluene shown in Figure 4-4 was

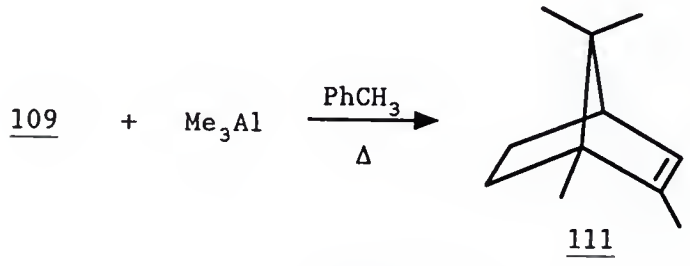


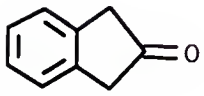
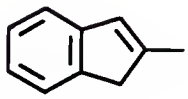
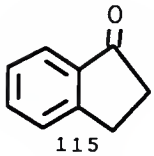
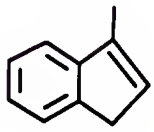
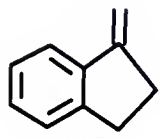
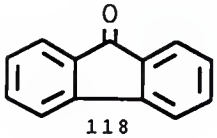
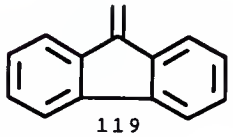
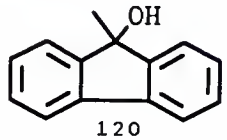
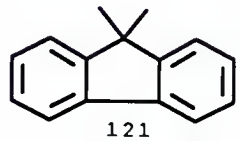
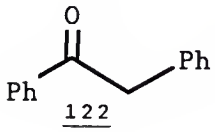
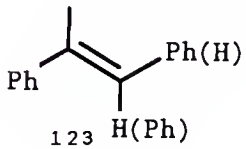
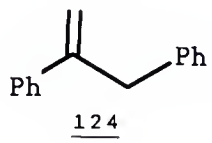
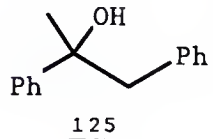
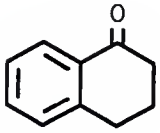
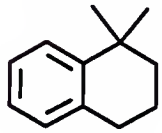
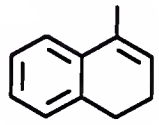
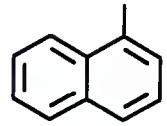
Figure 4-4

allowed to continue for 24 hr a hydrocarbon product, 2-methylcamphene, 111, was isolated in 81% yield. Noteworthy is the fact that the solvent had largely evaporated and the pot temperature had increased

overnight. This result prompted the investigations into the possible synthetic utility of this transformation as discussed herein.

A summary of the reactions carried out in this study can be found in Table 4-1. The reactions are

TABLE 4-1 Reaction of Trimethylaluminumon Various Ketones

Ketone	Procucts in Decreasing Concentration
 113	 114
 115	 116  117
 118	 119  120  121
 122	 123  124  125
 126	 127  128  129

run with 4.0 equivalents of Me_3Al in *m*-xylene at 150-210° C for up to 30 hours in a simple reflux apparatus. At the end of the reaction time most of the

solvent had evaporated to leave a brown oil that was washed with 10% hydrochloric acid (HCl) and extracted with diethyl ether (Et_2O). The various products realized include tertiary alcohols, alkenes, and *gem*-dimethylated hydrocarbons. In accordance with the results obtained, the ketones studied follow the same general reaction pathway: methyl addition to form the tertiary alcohol followed by elimination to form the alkene product(s). Exhaustive methylation products similar to those reported by Mole are also seen in some instances at higher reaction temperatures.

The most interesting and by far the most synthetically useful example demonstrated to date is the reaction of Me_3Al and (+)-*d*-camphor as shown in Figure 4-4 to yield 2-methylcamphene. A small amount of the tertiary alcohol 110 is seen if the reaction is stopped prior to completion or not heated strongly enough. No other products are seen by capillary GC in the reaction mixture in concentrations greater then one percent. Product determination was accomplished by ^1H and ^{13}C NMR and GC/MS. The one step isolation of 2-methycamphene is interesting because of the different alcohols that can subsequently be achieved, by various forms of hydroxylation reactions, and their potential use in natural product synthesis.

The other ketones presented in this study form the expected alkenes as the major product with the

only exception being α-tetralone. Table 4-1 shows the reactions and products obtained under the conditions found for optimum alkene formation. The reactions reported in the table were run under two different sets of conditions: 1) ~150° C for 30 hr and/or 2) ~200° C for 15 hr. As demonstrated in the camphor case, it appears that the reaction temperature is the major factor in determining the product distribution of the reactions. For example, the reaction of 2-indanone produced the methyl addition product exclusively at the lower temperature while at the elevated temperature only the one alkene product was realized.

The reaction of 1-indanone demonstrates the ability of the resultant alkenes to rearrange under the reaction conditions. This result is consistent with the extreme reaction conditions present, high temperature coupled with a strong Lewis acid. The presence of the isomeric alkenes was confirmed by ^{1}H NMR and GC/MS. The diagnostic information, in this case, was gleaned from the vinylic region of the ^{1}H NMR which clearly depicts resonances for the two isomeric alkenes.

A further example of this temperature effect may give an insight to the route of the *gem*-dimethylation reaction of fluorenone reported by Mole. In our hands fluorenone gave as the major product

9-methylenefluorene at the milder conditions. Also seen in the reaction mixture were the alcohol and dimethylation products, 41% and 12% respectively. It is believed that a longer reaction time would have resulted in more alkene by elimination of the alcohol. At the same time more of the dimethylation product could have resulted, this could possibly be alleviated by a decrease in the reaction temperature. However, at the elevated temperature 9,9-dimethylfluorene is the dominant product with only trace amounts of the alkene and unreacted starting material present, thus demonstrating the inability of the alcohol to survive under the reaction conditions.

This result prompts us to suggest that the dimethylation product seen in other studies results from the alkene as shown in Figure 4-5. In the cases where there are α-protons on either R or R′, rearrangement of the alkene can occur, as seen in the reaction of deoxybenzoin. Both the *cis*- and *trans*-stilbene type structures and the 1-methylene-1,2-diphenylethane structure are seen in the product mixture. Interestingly, the dimethylation product was noted in both reactions but to a lesser extent, with respect to total alkene, in the higher temperature reaction. This would lead one to consider that the intermediate responsible for dimethylation must form prior to rearrangement of the alkene species

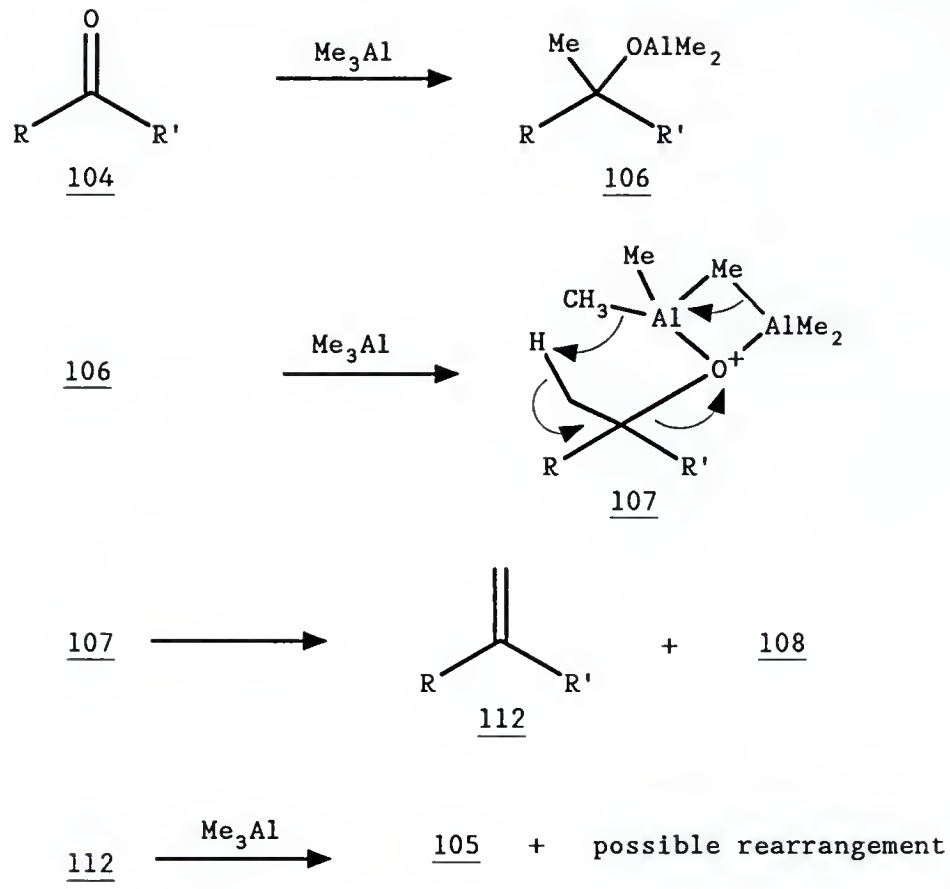


Figure 4-5

in order to form the *gem*-dimethylation product. Support for this assertion comes out of the Allen group.[36] They demonstrated the decrease in reactivity

$$HC{=}CH > HC{=}CHR > HC{=}CR > RHC{=}CHR$$

Figure 4-6

of alkenes toward alkylation as its substitution increases as shown in Figure 4-6.[36]

In stark contrast to the above results is the case of α-tetralone. At either set of conditions the major product isolated was that of the dimethylation reaction. Some alkene (23.6%) and 1-methylnapthalene (16.9%) were noted at the lower temperature; only trace amounts of these compounds were observed in the reaction mixture when subjected to the higher temperature conditions. It is believed that the isolation of the alkene in greater amounts is possible by variation of the reaction time and, most importantly, reaction temperature.

CHAPTER V

SUMMARY

A new synthetic route to vinyl oxiranes that is superior in some aspects to previous methods has been demonstrated in the second chapter of this work. This route utilizes the diphenylphosphinoyl group as an anchor to give stable crystalline intermediates rather than the volatile liquids encountered in other schemes. The structure of 42 was assigned the *cis* configuration through mechanistic, chemical and spectral considerations, and ultimately through single crystal X-ray analysis. Yields of the vinyl oxiranes 24 and 56 obtained by this sequence range from 55-65%. Although these non-optimized yields are somewhat lower than anticipated, it is believed that the advantages associated with this modified Horner-Wittig approach merit consideration for the generation of the more volatile vinyl oxiranes. Additionally, this work has spurred continued studies devoted to the extension of the use of the diphenylphosphinoyl group as a synthetically useful tool for the synthetic organic chemist.

The work contained in the third chapter of this dissertation, in conjunction with that of Cuevas, has presented the use of aluminum enolate methodology in organic synthesis. The scope and reactivity of these reagents has been investigated yielding favorable results and suggest continued investigation and exploitation of this methodology. Though the exact structure of Rathke alane has not yet been proven and, therefore, the details of the mechanism of reaction with vinyl oxiranes remain unclear, ample evidence exists to support the suggested "ice-tong" pathway for ring-opening. Continued studies in this area should include investigations incorporating chiral induction agents on the aluminum atom as well as continued efforts with the enolate.

The fourth section of this dissertation demonstrates a use of the Me_3Al species as an additionelimination reagent under thermal conditions. The key reaction demonstrated is the formation of 2-methylcamphene from camphor in a single, high-yielding step. This previously overlooked application demonstrates the need for continued expansion of the research into this field. Studies of more complex alkylaluminum reagents on structurally useful skeletons, e.g. camphor, may yield incredibly powerful synthetic tools.

CHAPTER VI

EXPERIMENTAL

General Experimental

Melting points were taken on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were performed by the University of Florida Spectroscopic Services. Proton and carbon NMR spectra were recorded on either of two instruments, a Varian VXR XL-300 or a General Electric QE-300, unless noted otherwise. Proton chemical shifts were recorded relative to the residual solvent peak (chloroform @ 7.26 ppm, unless otherwise noted). Carbon chemical shifts are reported relative to the deuteriochloroform resonance at 77.00 ppm. Coupling constants are reported in Hertz (Hz). Infra-red spectra were run on a Perkin-Elmer Model 1600 FT-IR spectrophotometer. Electron impact/low resolution mass spectra were obtained on a Finnigan MAT 4500 mass spectrometer at 70 eV. A Finnigan MAT 95 spectrometer was used for high resolution electron impact and chemical ionization exact mass determination.

Apparatus and Technique

All glassware used for air-sensitive reactions was flame dried under vacuum and filled with an inert atmosphere of either argon or nitrogen by successive purging and charging using a dual manifold vacuum line. Standard syringe technique was used for the introduction of liquid reagents and solutions to the reaction vessels. Purified samples were obtained by distillation, recrystallization, or flash column chromatography.[37]

Reagents and Solvents

The strength of the alkyl lithium reagents used was determined by titration with 2,5-dimethoxybenzyl-alcohol.[38] Tetrahydrofuran (THF), hexane, toluene, and diethyl ether, when used as reaction solvents, were distilled from sodium-benzophenone.[39] Diisopropyl amine and methylene chloride were distilled from calcium hydride.

1-(Diphenylphosphinoyl)methylcyclohexanol (45).

Cyclohexanone (1.17 g, 12.0 mmol) was added to a stirred solution of the lithium salt 44 (1.2 eq, 14.4 mmol) in THF (3o mL) at -78° C. The reaction was stirred at dry ice temperatures for 15 min before being allowed to warm slowly to room temperature where a solid began to precipitate. THe solid was filtered, dissolved in methylene chloride (CH_2Cl_2), dried over

magnesium sulfate ($MgSO_4$), and solvents removed to yield a white powder 45 (3.32 g, 10.6 mmol) with a m.p. = 163-166° C. ^1H NMR δ 7.75 (m, $4H_{Ar}$), 7.48 (m, $6H_{Ar}$), 4.82 (br s, $1H_{OH}$), 2.56 (d, J = 9.9 Hz, $2H_{CP}$), 1.67 (m, $4H_{ring}$), 1.29 (m, $6H_{ring}$). ^{13}C NMR δ 133.6 (d, J = 98.1, C_{ipso}), 131.8 (d, J = 2.8, C_{Ar}), 130.4 (d, J = 9.6, C_{Ar}), 128.7 (d, J = 11.8, C_{Ar}), 72.2 (d, J = 6.0, C_{OH}), 40.7 (d, J = 3.8, C_{P6}), 39.7 (d, J = 8.3, $C_{\alpha-OH}$), 25.4 (C_{ring}), 22.0 (C_{ring}). High Resolution Mass Spectrum (HR/MS) for $C_{19}H_{23}O_2P$ - 314.1430_{found}, 314.1436_{calc}; Fragmentation (70 eV): 315 (M + 1 [self C.I.], 26.1), 314 (M^+, 35.2), 296 (44.9), 271 (82.3), 258 (35.3), 215 ($Ph_2P(O)CH_2^+$, base), 201 ($Ph_2P(O)^+$, 79.5), 91 (24.5), 77 (41.5). Anal. Calcd: C, 72.60; H, 7.32. Found: C, 72.15; H, 7.39.

1-(Diphenylphosphinoyl)methylcyclohex-2-en-1-ol (41).

Methyldiphenylphosphine oxide (26.9 g; 0.124 mol) was dissolved in dry THF (100 mL) and cooled to 0° C under an Ar blanket. n-Butyl lithium (BuLi, 2.5 M, 49.6 mL; 0.124 mol) was added dropwise via syringe to yield a bright yellow-orange solution which was stirred an additional 15 min. Dropwise addition of the 2-cyclohexen-1-one (12.6 g; 0.131 mol) produced a blood-red solution, which after stirring a further 15 min, was quenched by addition of water (50 mL). The

reaction solution was extracted with methylene chloride (CH_2Cl_2, 3 x 100 mL), the organic layers combined, washed with brine and dried over magnesium sulfate ($MgSO_4$). Removal of the solvent left a white powder (35.98 g, 93 %), m.p.(acetone) 152-154° C.[12] ^1H NMR δ 7.80 (m, 4 H_{Ar}), 7.50 (m, 6 H_{Ar}), 5.72 (d, J = 10.2 Hz, 1 H_{vinyl}), 5.64 (dt, J_d = 10.2, J_t = 3.5, 1 H_{vinyl}), 5.10 (br s, 1 H_{OH}), 2.84 (dd, J = 15.2, 10.6, 1 H_{CP}), 2.65 (dd, (J = 15.2, 8.6, 1 H_{CP}), 2.10 - 1.40 (m, 6 H_{ring}). ^{13}C NMR δ 134.1 (d, J = 95.4 Hz, C_{ipso}), 133.9 (d, J = 95.2, C_{ipso}), 132.6 (d, J = 9.7, C_{vinyl}), 131.8 (d, J = 2.7, C_{Ar}), 130.5 (d, J = 9.5, C_{Ar}), 130.4(d, J = 9.6, C_{Ar}), 129.0 (s, C_{vinyl}), 128.8 (d, J = 11.9, C_{Ar}), 128.7 (d, J = 11.9, C_{Ar}), 70.2 (d, J = 5.3, C_{OH}), 40.4 (d, J = 69.0, C_p), 37.6 (d, J = 7.0, $C_{\alpha OH}$), 24.7 (s, $C_{\alpha\text{-}vinyl}$), 19.0 (s, C_{ring}). High Resolution Mass Spectrum (HR/MS) for $C_{19}H_{21}O_2P$ - 312.1272_{found}, 312.1279_{calc}; Fragmentation (70 eV): 313 (M + 1 [self C.I.], 42.2 %), 295 (base), 284 (27.7), 215 ($Ph_2P(O)CH_3^+$, 85.5), 202 ($Ph_2P(O)H^+$, 33.0), 91 (25.8), 77 (30.8). IR(cm^{-1}): 3500-3100 broad, 3063, 2980, 1438 (P-C), 1182, 1167. Anal. Calcd: C, 73.08; H, 6.73. Found: C, 72.93; H, 6.76.

1-(diphenylphosphinoyl)methyl-2,3-oxidocyclohexan-1-ol (42).

To a solution of 41 (4.00 g, 12.8 mmol) in

methylene chloride (CH_2Cl_2, 40 mL) at 0° C was added, with stirring, a solution of m-chloroperbenzoic acid (MCPBA, 65 %, 5.34 g, 30.9 mmol) in CH_2Cl_2 (25 mL) at approximately 1 drop per second. This solution was stirred for 24 hr at which time thin layer chromatography (TLC) indicated no starting material remained. The reaction was quenched with 0.32 M aqueous sodium thiosulfate (NaS_2O_3, 40 mL).The organic layer was then washed with 1.0 M NaOH followed by brine solution, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow-tinted oil. This oil was triturated with pentane to afford 42 (3.98 g, 12.1 mmol, 94.8 %) as a white solid: m.p. 120-124 °C ; ^1H NMR δ 7.80 (m, 4 H_{Ar}), 7.50 (m, 6 H_{Ar}), 4.39 (br s, 1 H_{OH}), 3.25 (d, J = 3.5 Hz, 1 H_{epox}), 3.17 (dt, J_d = 3.6, J_t = 1.2, 1 H_{epox}), 2.75 (16 line m, 2 H_{CP}), 1.96-1.11 (4 m, 6 H_{ring}). ^{13}C NMR δ 133.9 d, J = 99.7 Hz, C_{ipso}), 133.6 (d J = 99.7, C_{ipso}), 131.9 (3 lines, C_{Ar}), 130.5 (3 lines, C_{Ar}), 128.7 (4 lines, C_{Ar}), 70.9 (d, J = 4.6, C_{OH}), 58.3 (d, J = 9.6, C_{epox}), 54.8 (s, C_{epox}), 38.0 (d, J = 70.5, C_P), 34.4 (d, J = 5.8, $C_{\alpha OH}$), 22.6 (s, $C_{\alpha epox}$), 16.6 (s, C_{ring}). HR/MS for $C_{19}H_{21}O_3P$ - 328.1229_{found}, 328.1219_{calc}; Fragmentation (70 eV): 329 (M + 1 [self C.I.], 26.3 %), 328 (M^+, 8.7), 311 (12.8), 258 (24.1), 215 ($Ph_2P(O)CH_3^+$, 51.1), 202 ($Ph_2P(O)H^+$,base), 91 (12.9), 77(33.5). IR (cm^{-1}):

3600-3100 broad, 2987, 1437, 1166, 1119.

Preparation and attempted epoxidation of 1-(diphenylphosphinoyl)methyl-1-methoxycyclohex-2-ene (46).

Hydroxyalkene 41 (0.80 g, 2.6 mmol) was dissolved in 5 mL of dry THF and the solution cooled to 0° C. While stirring, potassium hydride (0.11 g, 2.8 mmol) was added in one portion and the resulting yellow solution was stirred for an additional 15 min. Addition of excess methyl iodide (MeI, 1.1g, 7.8 mmol) resulted in immediate disappearance of the yellow color. After further stirring (15 min) brine was added and the aqueous solution extracted with methylene chloride (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo to yield a thick, yellow oil. ^1H NMR of the crude oil showed complete conversion to the methyl ether, 46; ^1H NMR δ 7.75 (m, $4H_{Ar}$), 7.45 (m, $6H_{Ar}$), 5.83 (dt, J_d = 10.4 Hz, J_t = 3.9, H_{vinyl}), 5.68 (d, J = 10.4, H_{vinyl}), 2.99 (s, $3H_{OMe}$), 2.70 (d, J = 2.1, H_{CP}), 2.66 (d, J = 1.6, H_{CP}), 2.05-1.55 (m, $6H_{ring}$); ^{13}C NMR δ 135.1 (d, J = 99.7 Hz, C_{ipso}), 134.7 (d, J = 99.6, C_{ipso}), 131.7 (C_{vinyl}), 131.6 (d, J = 2.9, C_{vinyl}), 131.0 (d, J = 2.7, C_{Ar}), 130.7 (d, J = 9.2, C_{Ar}), 130.6 (d, J = 9.2, C_{Ar}), 128.5 (d, J = 12.0, C_{Ar}), 128.1 (d, J = 11.6, C_{Ar}), 128.0 (d, J = 11.7, C_{Ar}), 74.5 (d, J = 4.2, C_{OH}), 49.9 (C_{OMe}), 40.3 (d, J

= 69.9, C_P), 33.0 (d, J = 5.0, $C_{\alpha\text{-}COH}$), 24.7 ($C_{\alpha\text{-}vinyl}$), 19.3 (C_{ring}).

Without further characterization the crude methyl ether, 46, from above was treated with 1.5 equivalents of MCPBA (55 %) in CH_2Cl_2 at 0° C with slow warming to room temperature. Workup as in the epoxidation of 41 yielded a crude yellow oil on solvent removal which on ^1H NMR examination ($CDCl_3$) revealed a rather congested epoxide region (δ 3.15-3.30) suggesting a mixture of *cis* and *trans* isomers of the epoxide. The methoxy peak lies in the middle of this epoxide region, further complicating the interpretation. A 1:1 solvent mixture of benzene-d_6 and $CDCl_3$ did little to resolve the region. The ^{13}C NMR is very complex with peaks from the alkene 46 and what looks like two isomers of the epoxide.

1-(Diphenylphosphinoyl)methyl-1,2,3-trihydroxcyclohexane (49).

Attempts to recrystallize (3:1 EtOAc: hexane) the epoxide, 42, with heating (55° C) resulted in the formation of a difficultly soluble white powder, m.p. 183.5-187.5° C, and recovery of epoxide 42 as a yellow oil. Attempts to recrystallize the white solid were unsuccessful. 6: ^1H NMR δ 7.85 (m, 2 H_{Ar}), 7.70 (m, 2 H_{Ar}), 7.50 (m, 6 H_{Ar}), 4.94 (baseline roll, 1 H_{OH}), 3.76 (br s, 1 H_{OH}), 3.65 (ddd, J = 11.5, 8.8, and 4.5

Hz, 1 H_{C3-OH}), 3.29 (d, J = 8.8, 1 H_{C2-OH}), 2.78 (overlapping dd, J = 15.3, 14.2, 1 H_{CP}), 2.59 (dd, J = 15.4, 8.1, 1 H_{CP}), 2.02-1.21 (m, 6 H_{ring}). ^{13}C NMR δ *ipso* carbons not seen, 132.1 (d, J = 3.7 Hz, C_{Ar}), 130.9 (d, J = 9.6, C_{Ar}), 130.3 (d, J = 9.2, C_{Ar}), 128.8 (d, J = 12.0, C_{Ar}), 79.7 (d, J = 5.3, C_{2-OH}), 75.3 (d, J = 4.8, C_{1-OH}), 71.2 (s, C_{3-OH}), 40.0 (d, J = 68.9, C_P), 38.5 (d, J = 8.3, $C_{\alpha 1-OH}$), 31.3 (s, $C_{\alpha 3-OH}$), 18.9 (s, C_{ring}). HR/MS for $C_{19}H_{23}O_4P$ - 346.1330_{found}, 346.1370_{calc}; Fragmentation (70 eV): 347 (M + 1, [self C.I.], 49.8 %), 328 (M - 17, 9.6), 311 (7.6), 258 (21.2), 215 ($Ph_2P(O)CH_3^+$, 23.7), 202 ($Ph_2P(O)H^+$,base), 77 (19.3). IR(cm^{-1}): 3401, 3248, 2931, 1437, 1173, 1114, 1079, 979. Anal. Calcd: C, 65.89; H, 6.65. Found: C, 65.53; H, 6.65.

Formation of acetonide 52.

p-Toluenesulfonic acid monohydrate (5 mg) and 2,2-dimethoxypropane (3.0 g, 29 mmol) were refluxed in 5 mL benzene for 10 min and allowed to cool under an Ar blanket. Triol 49 (0.45 g, 1.3 mmol), dissolved in 10 mL of benzene and 2.5 mL of methylene chloride, was added and the reaction mixture was refluxed with stirring for 2 hr. TLC examination indicated a single component with a different R_f than that of the starting material. Solvent removal afforded a white powder (0.46 g, 1.2 mmol, 91.6 %), m.p.(acetone)

164-168° C. 8: ^{1}H NMR δ 7.80 (m, 4 H_{Ar}), 7.50 (m, 6 H_{Ar}), 4.74 (br s, 1 H_{OH}), 3.93 (ddd, J = 11.6, 9.1, and 4.0 Hz, 1 H_{C3-OH}), 3.08 (d, J = 9.0, H_{C2-OH}), 2.52 (dd, J = 15.2, 12.0, 1 H_{CP}), 2.52 (dd, J = 15.2, 8.2, 1 H_{CP}), 2.07 (br d, 1 H_{ring}), 1.93 (br d, 1 H_{ring}), 1.73-1.04 (m, including two methyl singlets at 1.45 and 1.25, 10 H). ^{13}C NMR (*ipso* carbons not seen) δ 131.8 (d, J = 2.8 Hz, C_{Ar}), 131.7 (d, J = 2.2, C_{Ar}), 130.5 (d, J = 9.1, C_{Ar}), 130.3 (d, J = 9.8, C_{Ar}), 128.7 (d, J = 11.5, C_{Ar}), 128.5 (d, J = 12.0, C_{Ar}), 108.7 (s, C_{acetal}), 85.6 (d, J = 9.9, C_O), 73.7 (d, J = 2.0, C_O), 73.1 (d, J = 6.3, C_O), 37.8 (d, J = 65.6, C_P), 37.3 (s, $C_{\alpha\text{-}acetal}$), 28.8 (s, $C_{\alpha\text{-}OH}$), 27.0 (s, CH_3), 26.7 (s, CH_3), 19.8 (s, C_{ring}). HR/MS (chemical ionization) for $C_{22}H_{28}O_4P$ - 387.1739_{found}, 387.1725_{calc}; Fragmentation (70 eV): 387 (M + 1, self C.I.), 347 (M - $CH_3C(O)CH_2$, 4.21 %), 328 (5.1), 310 (14.5), 258 (16.8), 215 ($Ph_2P(O)CH_3^+$, 33.1), 202 ($Ph_2P(O)H^+$, base), 155 (13.8), 125 (12.3), 77 (14.4). IR (cm^{-1}): 3330 (broad), 3074, 2932, 1712, 1590, 1439, 1175, 1112, 1081.

3-methylene-1,2-oxidocyclohexane (24).

Epoxide 42 (3.0 g, 9.2 mmol) was dissolved in 5 mL dry THF and warmed to 60° C with stirring. Sodium hydride (0.26 g, 11 mmol), previously washed with pentane, was suspended in 2 mL of dry THF and the

hydride slurry added slowly to the warm epoxide solution causing a color change from yellow to brown and evolution of hydrogen. Upon completion of hydride addition (20 min) the solution was allowed to stir for an additional 0.5 hr during which time a suspended solid formed. The solution was allowed to cool to room temperature and an equal volume of water was added to dissolve the solid. The resulting single phase solution was extracted with ether (3 x 5 mL) and the combined ether extracts were washed with 1 M NaOH and brine solutions. Drying ($MgSO_4$) and solvent removal in vacuo yielded a yellow tinted oil, 1.03 g (25% THF by ^1H NMR) 77 %. ^1H NMR δ 5.23 (dd, J = 1.4, 1.7 Hz, 1 H_{vinyl}), 5.11 (dd, J = 1.4, 1.5, 1 H_{vinyl}), 3.42 (d, J = 3.9, 1 H_{epox}), 3.38 (7 line m, 1 H_{epox}), 2.27 (m, 1 H_{ring}), 2.03 (m, 2 H_{ring}), 1.83 (m, 1 H_{ring}), 1.59 (m, 1 H_{ring}), 1.40 (m, 1 H_{ring}). ^{13}C NMR δ 142.6 (C_{vinyl}), 116.1 (C_{vinyl}), 55.1 (C_{epox}), 54.2 (C_{epox}), 28.6 (C_{ring}), 24.0 (C_{ring}), 19.7 (C_{ring}). LR/MS fragmentation (70 eV) 110 (M^+, 28.2 %), 95 (40.4), 81 (57.8), 67 (46.5), 53 (43.3), 41 (79.1), 39 (base).

1-(Diphenylphosphinoyl)methyl-3-methylcyclohex-2-en-1-ol (54).

To a cooled solution (0° C) of diphenylmethyl-phosphine oxide (13.9 g, 64.4 mmol) in THF (50 mL)

under argon was added a hexane solution of BuLi (2.5 M, 25.8 mL, 64.5 mmol). The resulting golden yellow solution was stirred for an additional 20 min and then cooled to -25° C, whereupon 3-methylcyclohex-2-en-1-one (7.09 g, 64.4 mmol) was added dropwise to give a red-orange solution. Stirring was continued at -25° C for 20 min before the solution was allowed to warm slowly to room temperature. After a total of 6 hr stirring at room temperature the reaction flask was opened to the atmosphere and stirring continued until color abatement. Concentration of the reaction mixture in vacuo followed by addition of water resulted in the precipitation of a white solid (20.2 g, 97.1 %) which was recrystallized from acetone to yield 17.9 g (54.9 mmol) of 54: 126-129° C; ^{1}H NMR δ 7.69 (m, 4 H_{Ar}), 7.41 (m, 6 H_{Ar}), 5.30 (s, 1 H_{OH}), 4.92 (s, 1 H_{vinyl}), 2.63 (dd, J = 15.0, 8.4 Hz, 1 H_{CP}), 2.50 (dd, J = 15.0, 10.6, 1 H_{CP}), 1.72 (m, 4 H_{ring}), 1.43 (m, methyl singlet at 1.42, 5 H ,2 H_{ring} and CH_3). ^{13}C NMR δ 136.7 (s, C_{vinyl}), 133.9 (d, J = 99.6 Hz, C_{ipso}), 133.6 (d, J = 98.1, C_{ipso}), 131.5 (d, J = 3.0, C_{Ar}), 131.4 (d, J = 3.1, C_{Ar}), 130.3 (d, J = 8.2, C_{Ar}), 130.1 (d, J = 9.3, C_{Ar}), 128.5 (d, J = 11.9, C_{Ar}), 128.4 (d, J = 11.8, C_{Ar}), 127.5 (d, J = 9.8, C_{vinyl}), 70.5 (d, J = 5.0, C_{OH}), 40.6 (d, J = 69.0, C_P), 36.9

(d, J = 6.7, $C_{\alpha\text{-}OH}$), 29.4 (s, $C_{\alpha\text{-}vinyl}$), 23.1 (s, CH_3), 19.1 (s, C_{ring}). HR/MS for $C_{20}H_{23}O_2P$ - 326.1422_{found}, 326.1436_{calc}; Fragmentation (70 eV): 327 (M + 1, self C.I., 5.7 %), 309 (M - OH, base), 215 ($Ph_2P(O)CH_3^+$, 80.5), 202 ($Ph_2P(O)H^+$, 33.1), 91 (28.5), 77 (34.6). IR (cm^{-1}): 3419 (broad), 3058, 2938, 1438, 1160. Anal. Calcd: C, 73.61; H, 7.06. Found: C, 73.54; H, 7.10.

1-(Diphenylphosphinoyl)methyl-3-methyl-2,3-oxido-cyclohexan-1-ol (55).

The phosphinoylmethylcyclohexenol 54 (15.9 g, 48.7 mmol) was dissolved in 100 mL of methylene chloride and the solution cooled to 0° C. MCPBA (60 %, 19.6 g, 68.2 mmol), suspended in methylene chloride (100 mL) was added in portions over a 1 hr period such that any heat generated by the addition was allowed to dissipate before further addition was carried out. The reaction was stirred (42 Hr) until TLC showed complete consumption of the starting material. Quenching was accomplished by the addition of $Na_2S_2O_3$ at room temperature with stirring (15 min). Usual workup afforded a sticky white solid which on trituration with pentane gave 14.5 g (42.4 mmol, 87 %) of a white solid, m.p. 115-120° C: ^1H NMR δ 7.82 (m, 6 H_{Ar}), 7.48 (m, 4 H_{Ar}), 4.16 (br s, 1 H_{OH}), 2.99 (s, 1 H_{epox}), 2.64 (16 line m, 2 H_{CP}), 2.25-1.30 (m, 6

H_{ring}), 1.05 (s, 3 H_{methyl}). ^{13}C NMR δ 134.2 (d, J = 111 Hz, C_{ipso}), 134.1 (d, J = 114, C_{ipso}), 131.9 (3 lines C_{Ar}), 130.5 (3 lines, C_{Ar}), 128.6 (3 lines, C_{Ar}), 70.8 (d, J = 3.0, C_{OH}), 65.2 (d, J = 9.1, C_{epox}), 61.1 (s, C_{epox}), 38.9 (d, J = 70, C_P), 34.7 (d, J = 5.3, $C_{\alpha-OH}$), 28.2 (s, $C_{\alpha-epox}$), 23.8 (s, C_{methyl}), 16.9 (s, C_{ring}). HR/MS for $C_{20}H_{23}O_3P$ - 342.1392_{found}; 342.1385_{calc}; Fragmentation (70 eV) 342 (M^+, 5.1 %), 328 (1.7), 323 (16.5), 258 (20.1), 215 ($Ph_2P(O)CH_3^+$, base), 202 ($Ph_2P(O)H^+$, 61.0), 91 (8.1). IR (cm^{-1}): 3363 (broad), 2938, 1437, 1157, 1119.

1-(Diphenylphosphinoyl)methyl-1,2,3-trihydroxy-3-methylcyclohexane (57).

Upon chromatography of the above oxirane 55, a late eluting compound was realized in the form of large colorless crystals, m.p. (EtOAc) 166-168° C. ^1H NMR δ 7.82 (m, 2 H_{Ar}), 7.69 (m, 2 H_{Ar}), 7.48 (m, 6 H_{Ar}), 4.46 (d, J = 5.7 Hz, 1 H), 4.13 (s, 1 H), 3.52 (d, J = 5.8, 1 H), 2.95 (dd, J = 15.3, 13.1, 2 H, H_{CP} and H_{OH}), 2.62 (dd, J = 15.4, 8.5, 1 H_{CP}), 1.90-1.26 (m, 6 H_{ring}), 1.24 (s, 3 H_{methyl}). ^{13}C NMR δ 133.7 (d, J = 100.9 Hz, C_{ipso}), 132.7 (d, J = 99, C_{ipso}), 131.9 (d, J = 3.3, C_{Ar}), 131.8 (d, J = 3.1, C_{Ar}), 130.7 (d, J = 9.6, C_{Ar}), 130.3 (d, J = 9.6, C_{Ar}), 128.7 (d, J = 12.6, C_{Ar}), 80.0 (d, J = 6.1, C_{C2-OH}), 75.2 (d, J = 5.3, C_{C1-OH}), 73.4 (s, C_{C3-OH}), 39.5 (d,

J = 69.1, C_P), 37.6 (d, J = 6.9, $C_{\alpha\text{-}C1\text{-}OH}$), 36.8)s, $C_{\alpha\text{-}C3\text{-}OH}$), 23.5 (s, C_{methyl}), 18.7 (s, C_{ring}). HR/MS (chemical ionization) mass for $C_{20}H_{25}O_4P$ - 361.1571_{found}, 361.1569_{calc}; Fragmentation (70 eV): 361 (M + 1, 99.7 %), 342 (M - H_2O, 22.0), 324 (14.9), 271 (15.7), 258 (14.6), 243 (11.4), 215 ($Ph_2P(O)CH_3^+$, 56.7), 202 ($Ph_2P(O)H^+$, base). IR (cm^{-1}): 3460 (broad), 3342 (broad), 2943, 1431, 1167, 1120. Anal. Calcd: C, 66.66; H, 6.94. Found: C, 66.63; H, 7.10.

1-Methyl-3-methylene-1,2-oxidocyclohexane (56).

To a solution of potassium hydride (1.54 g, 38.5 mmol) in 20 mL of dry THF warmed to 60 ° C was added a CH_2Cl_2 (100 mL) solution of epoxide 55 (12.0 g, 35.1 mmol) via cannula transfer. An immediate color change of the solution from colorless to a brown accompanied this addition. Continued addition was carried out in such a way as to minimize foaming due to gas evolution. After addition of 3b was completed the solution was stirred for an additional 2.5 Hr and then cooled to room temperature. Cooling led to the precipitation of a white solid. The reaction was quenched by the addition of aqueous K_2CO_3 (1.1 eq) and the aqueous mixture extracted with ether. The combined organic layers were washed with brine and dried ($MgSO_4$). Analysis of the etheral solution by GC/MS showed the presence of the desired methylene

oxirane 56 as the predominant component other than THF. Distillation (b.p. 30-32° C at 3 mmHg) provided 2.82 g of 1b (65 % yield): ^{1}H NMR δ 5.16 (br d, J = 1.4 Hz, H_{vinyl}), 5.05 (dd, J = 3.2, 1.6, H_{vinyl}), 3.21 (s, H_{epox}), 2.23 (m, 1 H_{ring}), 1.94 (m, 2 H_{ring}), 1.53 (m, 3 H_{ring}), 1.33 (s, 3 H_{methyl}). ^{13}C NMR δ 142.9 (C_{vinyl}), 115.9 (C_{vinyl}), 62.2 (C_{epox}), 59.5 (C_{epox}), 29.4 (C_{ring}), 28.3 (C_{ring}), 23.3 (C_{methyl}), 19.9 (C_{ring}). LR/MS Fragmentation (70 eV) 124 (M^{+}, 9.6), 109 (M - CH_3, 21.1), 95 (16.8), 81 (50.4), 55 (30.9), 43 (base).

Preparation of the C-methylation product 64.

One equivalent of BuLi (2.4 M, 0.5 mL; 1.2 mmol) was added to 41 (0.39 g; 1.2 mmol) dissolved in dry THF at 0° C to yield a bright yellow solution. One additional drop of the BuLi beyond 1 eq turned the solution orange in color which darkened with continued addition up to 2 eq. This solution of the dianion was stirred for 15min and then quenched with MeI (1.2 g, 7 eq) to give a colorless solution. A white, waxy, solid was isolated (0.35 g, 86 % yield). The crude ^{1}H NMR of the solid showed it to be the C-methylation product 64.

Preparation of *tert*-butylpropioate.

Propionyl chloride (74.6 g, 0.806 mol) was slowly added to a stirred ethereal solution of *tert*-butanol

(65.2 g, 0.881 mol) and N,N-dimethylaniline (110 g, 0.909 mol) to yield a pale blue solution that darkened over time to a dark blue. The reaction was quenched after 30 hr by careful addition of water (30 mL) then the mixture was extracted with ether (2 X 15 mL). The organic layers were combined and washed successively with 10% HCl (6 X 5 mL), saturated $NaHCO_3$ (3 x 5 mL), and brine (2 X 10 mL) and dried over $MgSO_4$. Distillation through a Vigreaux column afforded the *tert*-butyl propionate as a colorless liquid, b. p. 117-120° C (lit. 119-121° C[40]), 69.0 g, 65.7%. ^1H NMR δ 2.23 (q, 2H), 1.44 (s, 9H), 1.08 (t, 3H). ^{13}C NMR δ 173.7 (C_{ester}), 79.7 (C_{OR}), 28.6 ($C_{\alpha\text{-}C=O}$), 27.9 (C_{methyl}), 9.00 ($C_{\beta\text{-}C=O}$).

Preparation of 1-adamantylacetate (99).

To 20 mL anhydrous triethylamine was added 1-adamantanol (10 g, 65.7 mmol), N,N-dimethyl-aminopyridine (DMAP, 20 mg), and acetic anhydride (14.8 g, 144.6 mmol) and the resulting mixture was heated with stirring to 90-95° C under an argon atmosphere for 30 hr. The reaction solution was concentrated on the rotary evaporator to give a yellow oil. The oil was taken up in ether and washed with 1 N sodium hydroxide (NaOH) and brine and dried over $MgSO_4$. Concentration under vacuum gave a clear oil that crystallized upon sitting to give colorless

needles (12.33 g, 96% yield, m.p. 31.5-32.0° C, lit. 32.5-33.5° C).[41] ^{1}H NMR (ppm): 2.07, broad, irregular d, 6 H; 1.89, s, 3 H; 1.64, s, 3 H; 1.56, broad, irregular d, 6 H. ^{13}C NMR (ppm): 170.3, 80.2, 41.3, 36.2, 30.8, 22.7 . Mass Spectrum: 194 (M^{+}, 2.25%), 134 (base), 95 (36.0), 92 (73.5), 79 (23.42), 43 (41.5).

General procedure for the reaction of aluminum enolates on electrophiles.

The aluminum enolate reactions were carried out with a 2.0 molar excess of the organoaluminum species (3.0 eq alane to 1.0 eq of the electrophile) except where noted. Diisopropyl amine at 0° C was dissolved in hexane and BuLi added to it dropwise to generate the lithium diisopropyl amide which was then stirred for 30 min. The dropwise addition of the ester (*tert*-butyl acetate, *tert*-butyl propionate, or 1-adamantyl acetate) was carried out at -78° C and the resulting enolate was stirred for 30 min before warming to 0°C and opening to vacuum to remove the reaction solvents. The lithium salt obtained was pumped on for 30-60 min before being dissolved in THF and cooled to dry ice/acetone temperature. The dialkylchloroalane was added dropwise keeping the temperature below -60° C after which the electrophile (epoxide, ketone, or aldehyde) was immediately added,

dropwise. The reaction was generally allowed to stir for one hour before being quenched via cannula transfer into a rapidly stirring solution of 10% HCl and ice. The reaction mixture was extracted with diethyl ether, washed with water and brine, dried with $MgSO_4$ and solvents removed in vacuo to yield the hydroxyester.

Reaction of RkeAl 6 with 3-methylene-1,2-oxidocyclohexane 24.

The oxirane 24 (0.179 g, 1.63 mmol) was reacted under three stoichiometric ratios with the Rathke metals; the results of these studies are collected in Table 3-1. The yield of the hydroxy ester 25 was determined by capillary GC analysis against an internal standard (tridecane). ^1H NMR δ 4.82 (s, $1H_{vinyl}$), 4.68 (s, $1H_{vinyl}$), 3.27 (br s, $1H_{OH}$), 2.55 (m, $1H_{\alpha\text{-}OH}$), 2.41 (m, $2H_{\alpha\text{-}C=O}$), 2.18 (dt, J = 17.1, 7.6, $1H_{allylic}$), 1.94 (m, $2H_{ring}$), 1.70 (m, $2H_{ring}$), 1.39 (m, $2H_{ring}$), 1.35 (s, $9H_{t\text{-}Bu}$). ^{13}C NMR δ 172.9 (C_{ester}), 148.3 (C_{vinyl}), 108.3 (C_{vinyl}), 80.5 (C_{OR}), 74.3 (C_{OH}), 48.0 ($C_{allylic}$), 35.9 (C_{ring}), 34.8 (C_{ring}), 34.1 (C_{ring}), 28.0 ($C_{t\text{-}Bu}$), 24.4 ($C_{\alpha\text{-}C=O}$).

Ring opening to form chlorohydrin 79 and glycol 80 from oxirane 24.

The ring opened products (79, 80) were formed from 24 in two different ways: 1) reaction of 24 (0.10 g, 0.93 mmol) with Et_2AlCl (0.54 mL, 0.93

mmol) in THF at -65° C for 25 min followed by an aqueous workup and 2) a THF solution of 24 (0.12 g, 1.1 mmol) was subjected to standard dilute acid workup conditions (5 mL 10% HCl, ~50 g ice). Both reactions were extracted with ether (3 X 25 mL), washed with brine (1 X 10 mL), and dried over $MgSO_4$. The products were separated by gradient elution flash column chromatography (hexane to EtOAc). The chloroalane reaction favored formation of the later eluting glycol 80 (1:2.1) while the workup conditions produced more of the chlorohydrin 79 (1.6:1). 79: ^1H NMR δ 5.24 (s, $1H_{vinyl}$), 5.00 (s, $1H_{vinyl}$), 4.27 (d, J = 8.6 Hz, $1H_{allylic}$), 3.62 (m, $1H_{\alpha\text{-}OH}$), 2.2.48 (m, $2H_{ring}$), 2.18 (m, $1H_{ring}$), 2.04 (m, $1H_{ring}$), 1.76 (m, $1H_{ring}$), 1.53 (m, $1H_{ring}$). ^{13}C NMR δ 143.9 (C_{vinyl}), 112.2 (C_{vinyl}), 75.0 (C_{OH}), 68.7 (C_{Cl}), 33.4 (C_{ring}), 31.4 (C_{ring}), 23.3 (C_{ring}). 80: 5.02 (br s, $1H_{vinyl}$), 4.86 (br s, $1H_{vinyl}$), 3.88 (d, J = 8.3, $1H_{C2\text{-}OH}$), 3.36 (m, $1H_{C1\text{-}OH}$), 2.78 (br s, $1H_{OH}$), 2.59 (br s, $1H_{OH}$), 2.37 (m, $1H_{ring}$), 2.03 (m, $2H_{ring}$), 1.76 (m, $2H_{ring}$), 1.49 (m, $1H_{ring}$), 1.32 (m, $2H_{ring}$). ^{13}C NMR δ 148.6 (C_{vinyl}), 107.2 (C_{vinyl}), 78.8 (C_{OH}), 77.1 (C_{OH}), 34.6 (C_{ring}), 33.4 (C_{ring}), 25.2 (C_{ring}).

Formation of hydroxyester 81 from cyclohexanone (43).

The hydroxyester 81 was formed from cyclohexanone in two ways: 1) by action of 1.0 eq Rathke's salt 4

to give 38.5% conversion (GC) and 2) reaction with 1.0 eq of RkeAl 6 to give 76.7% conversion (GC). The procedure followed was as outlined in the general procedure above. 81: ^{1}H NMR δ 3.63 (s, $1H_{OH}$), 2.38 (s, $2H_{\alpha\text{-}C=O}$), 1.66 (m, $4H_{ring}$), 1.47 (s, $9H_{methyl}$), 1.44 (m, $2H_{ring}$), 1.29 (m, $4H_{ring}$). ^{13}C NMR δ 172.0 (C_{ester}), 81.4 (C_{OR}), 70.0 (C_{OH}), 46.3 ($C_{\alpha\text{-}C=O}$), 37.5 (C_{ring}), 28.2 (C_{methyl}), 25.7 (C_{ring}), 22.1 (C_{ring}).

Reaction of RkeAl 6 with benzaldehyde (85).

Benzaldehyde (1.76 g, 16.6 mmol) was added to a -65° C solution of the Rathke alane (20.0 mmol) and excess Et_2AlCl (6.6 mmol). No change was noted on the reaction mixture composition after 15 min reaction time; the reaction was worked up as described in the general RkeAl procedure above to yield, after Kugelrohr distillation (2.40 g, 10.8 mmol), 86: ^{1}H NMR δ 7.38 (m, $5H_{Ar}$), 5.17 (br s, $2H_{\alpha\text{-}Ar\ \&\ OH}$), 2.62 (br d, $2H_{\alpha\text{-}C=O}$), 1.43 (s, $9H_{t\text{-}Bu}$).

Reaction of RkeAl 6 with anisaldehyde (89).

Anisaldehyde (2.27 g, 16.6 mmol) was added to a -65° C solution of the Rathke alane (20.0 mmol) and excess Et_2AlCl (6.6 mmol). No change was noted on the reaction mixture composition after 15 min reaction time; the reaction was worked up as described in the general RkeAl procedure above to yield 90 after column chromatography (4% EtOAc in CH_2Cl_2): ^{1}H NMR δ 7.27

(d, J = 13.3 Hz, $2H_{Ar}$), 6.84 (d, J = 13.3, $2H_{Ar}$), 5.00 (m, $1H_{\alpha-Ar}$), 3.61 (br s, $1H_{OH}$), 2.62 (irr t, $2H_{\alpha-C=O}$), 1.43 (s, $9H_{t-Bu}$).

Reaction of MeRkeAl 91 with 3-methylene-1,2-oxido-cyclohexane (24).

This reaction resulted in the formation of two isomers in a 1.2:1 ratio (0.30 g, 68%); the spectral data is listed with what is believed to be isomeric signals in brackets. ^{1}H NMR δ 4.92 [4.79] (s, $1H_{vinyl}$), 4.84 [4.71] (s, $1H_{vinyl}$), 3.83 (dq, $1H_{\alpha-OH}$), 3.71 [3.60] (t, $1H_{allylic}$), 2.66 (m, $1H_{\alpha-C=O}$), 1.80-1.40 (m, $6H_{ring}$), 1.36 (s, $9H_{t-Bu}$), 1.11 [0.94] (d, J = 8.24 Hz, $3H_{Methyl}$). ^{13}C NMR δ 175.2 [173.8] (C_{ester}), 146.5 [145.2] (C_{vinyl}), 113.6 [111.8] (C_{vinyl}), 80.4 [79.8] (C_{OR}), 69.6 [69.0] ($C_{\alpha-OH}$), 54.5 [53.4] ($C_{allylic}$), 40.6 [40.0] (C_{ring}), 32.5 [31.1] (C_{ring}), 28.7 [28.2] (C_{ring}), 28.0 (C_{t-Bu}), 22.5 [21.9] ($C_{\alpha-C=O}$), 16.0 [14.1] (C_{Methyl}).

Reaction of AdmAl 100 with cyclohexanone (43).

The general aluminum enolate reaction procedure was followed with 100 (5.45 mmol) on cyclohexanone (0.104 g, 1.02 mmol). Following workup, the crude reaction product mixture was dissolved in methanol (15 mL) and aqueous NaOH (5 mL, 6 M) and warmed to a gentle reflux for 3.5 hr. Upon cooling the reaction mixture pH was lowered to ~10 by addition of 10% HCl

and extracted with ether (2 X 15 mL) to remove the 1-adamantanol. Continued acidification followed by ether extraction (2 X 15 mL), drying ($MgSO_4$), and solvent removal in vacuo to give a yellow oil 101 (0.12 g, 0.41 mmol, 40%). ^1H NMR δ 6.34 (baseline roll), 2.53 (s, $2H_{\alpha-C=O}$), 1.68 (m, $4H_{ring}$), 1.49 (m, $4H_{ring}$), 1.31 (m, $2H_{ring}$). ^{13}C NMR δ 176.8 ($C_{C=O}$), 70.6 (C_{OH}), 45.0 ($C_{\alpha-C=O}$), 37.2 (C_{ring}), 25.4 (C_{ring}), 21.9 (C_{ring}).

Reaction of AdmAl 100 with benzaldehyde (85).

The general aluminum enolate reaction procedure was followed with 100 (3.06 mmol) on benzaldehyde (0.115 g, 1.00 mmol). Following workup, the crude reaction product mixture was dissolved in methanol (15 mL) and aqueous NaOH (5 mL, 6 M) and warmed to a gentle reflux for 3.5 hr. Upon cooling the reaction mixture pH was lowered to ~10 by addition of 10% HCl and extracted with ether (2 X 15 mL) to remove the 1-adamantanol. Continued acidification followed by ether extraction (2 X 15 mL), drying ($MgSO_4$), and solvent removal in vacuo to give a yellow oil 102 (0.11 g, 0.37 mmol, 37%). ^1H NMR δ 7.27 (m, $5H_{Ar}$), 6.30 (baseline roll), 5.06 (dd, J = 9.3, 4.1 Hz, $1H_{benzyl}$), 2.68 (m, $2H_{\alpha-C=O}$). ^{13}C NMR δ 176.7 ($C_{C=O}$), 142.1 (C_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 125.7 (C_{Ar}), 70.3 (C_{OH}), 43.1 ($C_{\alpha-C=O}$).

Reaction of AdmAl 100 with 1-methyl-3-methylene-1,2-oxidocyclohexane (56).

The general aluminum enolate reaction procedure was followed with 100 (5.45 mmol) on the vinyl oxirane 56 (0.23 g, 1.8 mmol). Following workup, the crude reaction product mixture was dissolved in methanol (15 mL) and aqueous NaOH (5 mL, 6 M) and warmed to a gentle reflux for 3.5 hr. Upon cooling the reaction mixture pH was lowered to ~10 by addition of 10% HCl and extracted with ether (2 X 15 mL) to remove the 1-adamantanol. Continued acidification followed by ether extraction (2 X 15 mL), drying ($MgSO_4$), and solvent removal in vacuo to give an off-white solid (m.p. 125-127.5° C, 0.10 g, 0.54 mmol, 30%). ^1H NMR δ 5.0 (baseline roll), 4.86 (s, $1H_{vinyl}$), 4.69 (s, $1H_{vinyl}$), 2.78 (dd, J = 14, 4 Hz, $1H_{\alpha\text{-}C=O}$), 2.49 (dd, J = 14, 9, $1H_{\alpha\text{-}C=O}$), 2.20 (m, $4H_{ring}$), 1.72 (dt, J = 10, 2, $1H_{allylic}$), 1.62 (m, 2H), 1.10 (s, $2H_{ring}$). ^{13}C NMR δ 178.0 ($C_{C=O}$), 147.7 (C_{vinyl}), 109.4 (C_{vinyl}), 73.7(C_{OH}), 51.1 ($C_{allylic}$), 40.2 ($C_{\alpha\text{-}C=O}$), 36.0 (C_{ring}), 34.2 (C_{ring}), 32.3 (C_{ring}), 30.7 (C_{methyl}).

General procedure for the reaction of trimethyl-aluminum with ketones.

The ketone (1.38 mmol) is dissolved in 2 mL of dry *m*-xylene in round bottom flask. A blanket of Ar is maintaned throughout the duration of the reaction.

The Me_3Al hexane solution (5.60 mmol, 4.0 eq) is added using standard syringe technique at room temperature. After the evolution of heat and gas is complete the reaction flask is heated in a sand bath to the desired reaction temperature for the appropriate length of time. Upon completion the reaction is alloiwed to cool and an additional 3 mL of xylene is added. The reactions are quenched by pouring over a solution of 10 % HCl and ice. Ether extraction, drying with $MgSO_4$, and removal of solvent under reduced pressure complete the work-up. An etheral solution is made up for GC and CG/MS analysis. Product identification was made through comparison of the EI/MS to published spectral data.[42] It is necessary to note that the reported yields are uncorrected GC percentages unless otherwise noted..

Trimethylaluminum reaction with camphor (109).

The sole product realized was 2-methylcamphene: Mass Spectrum: 150 (M^+, 13.3 %), 135 (M - CH_3, 28.3), 121 (15.0), 107 (82.9), 93 (59.4), 79 (87.8), 41 (base). ^1H NMR δ 4.62-4.54 (d of m, 1 H) ^{13}C NMR δ 158.9 (C_{alkene}), 100.5 (C_{alkene}), 44.3 (C_{methyl}), 36.5 ($C_{methylene}$), 34.7 ($C_{methylene}$), 29.2 ($C_{methine}$), 27.5 (C_{quat}), 22.2 (C_{quat}), 19.1 (C_{methyl}), 18.4 (C_{methyl}), 12.0 (C_{methyl}).

Trimethylaluminum reaction with 2-indanone (113).

At a reaction temperature of 150° C for 24 Hr the only product isolated was the 3° alcohol resulting from methyl addition to the carbonyl. Mass Spectrum: 148 (M^+, 15.6 %), 105 (M - $COCH_3$, 54.4), 91 ($C_7H_7^+$, 8.2), 43 (base). Under the harsher conditions of a reaction temperature of 200° C for 15 Hr the sole product isolated was the alkene 114. Mass Spectrum: 130 (M^+, base), 115 (M - CH_3, 78.6%), 64 (34.8), 51 (26.9).

Trimethylaluminum reaction with 1-indanone (115).

The reaction was run at 150° C for 34 Hr and gave a product mixture 4:1 of the two possible alkenes. Mass Spectrum: (Major, 116) 130 (M^+, base), 115 (M - CH_3, 77.9 %), 63 (15.0), 51 (17.9); (Minor, 117) 130 (M^+, base), 115 (M - CH_3, 53.5%), 64 (11.8), 51 (17.1). ^1H NMR δ (peaks attributed to major isomer 116 are underlined): 7.45-7.10 (Aromatic), 6.27 (br s), 5.53 (t), 5.10 (t), 3.37 (t), 2.93-2.66 (m), 2.24 (dd).

Trimethylaluminum reaction with Fluorenone (118).

The alkene 119 is the major product seen at the lower temperature (46 % with 41 % ROH and 12 % dimethylation) while the dimethylation product 121 is dominant at the elevated temperature (trace amounts of the alkene noted). Mass Spectrum: 119 178 (M^+,

base), 152 (M - C_2H_2. 13.5 %), 89 (27.0), 76 (37.6); 120 196 (M^+, 23.8), 181 (M - CH_3, base), 152 (35.6), 91 (22.9), 76 (54.1); 121 194 (M^+, 35.0), 179 (M - CH_3, base), 152 (9.6), 89 (38.6), 76 (21.3).

Trimethylaluminum reaction with Deoxybenzoin (122).

Lower temperature reaction conditions gave a mixture of three alkenes, 74.7 % (1:3.4:3.3; *cis*-123:124:*trans*-123), and the dimethylation product (25.3 %). The higher temperature conditions afforded the same products but in different ratios and concentrations: alkenes, 89.5 % (1:0.56:0.37); dimethylation, 10.5 %. Compound 124 was tentatively assigned the structure shown based on its fragmentation as no published data was forthcoming. Mass Spectrum: *cis*-123 194 (M^+, 76.1 %), 179 (M - CH_3, base), 115 (41.7), 89 (22.9), 77 (24.1), 51 (27.3); *trans*-123 194 (M^+, 46.2 %), 179 (M - CH_3, 33.5), 116 (51.7), 103 (M - CH_2Ph, base), 91 (27.3), 77 (50.3); (124) 194 (M^+, 80.0 %), 179 (M - CH_3, base), 115 (42.9), 89 (26.5), 77 (20.0), 51 (22.1); 125 210 (M^+, 0.06 %), 152 (0.81), 119 (M - CH_2Ph, base), 103 (3.55), 91 (58.7), 41 (23.9).

Trimethylaluminum reaction with α-Tetralone (126).

The dimethylation product was the major product seen at either set of conditions; 59.5 % with 23.6 % alkene and 16.9 % 1-methylnapthalene at the lower

temperature and only trace alkene and methylnapthalene at the elevated temperatures. Mass Spectrum: 127 160 (M^+, 16.5 %), 145 (M - CH_3, base), 117 (18.8), 91 (15.3); 128 144 (M^+, 49.3 %), 129 (M - CH_3, base), 115 (14.4), 43 (32.9); 129 142 (M^+, base), 115 (29.5 %), 71 (14.6), 43 (17.8).

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BIOGRAPHICAL SKETCH

Curtis R. Campbell was born on October 30, 1963, in Beaver, Pennsylvania. He recieved a B.S. in chemistry from the Pennsylvania State University in May of 1986. The freshman and sophomore years of his undergraduate studies were spent at the Beaver Campus of Penn State where he worked part time in a quality control lab. That work experience convinced him to further his education beyond the B.S. due to the limitations to advancement and lack of responsibility. The summers after his junior and senior years were spent working for the Mobay Corporation in Pittsburgh where he got his first taste of the industrial world. The lure of warmer climes brought him to the University of Florida where he quickly picked up the sport of cave diving in the many springs of the area. He completed 99 penetrations without incident before he was awarded a fellowship from the Division of Sponsored Research that focused his energies on his research. Over the years his area of interest has swung toward environmental organic chemistry and the fate of pollutants in the environment which has lead to a position with Environmental Science and Engineering in Gainesville starting in January 1992.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Chemistry

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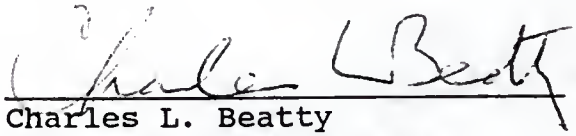

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This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1991

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Dean, Graduate School